

Appendix Document

S.19 Calculation Algorithm/Measure Logic Diagram

$$\frac{A \text{ (\# of patients meeting numerator criteria)}}{PD \text{ (\# patients in denominator)} - C \text{ (\# patients with valid denominator exclusions)}}$$

S.25 Data Source or Collection Instrument

DATA COLLECTION TOOL

To assist with the data collection at each physician practice site, an On-Site Adjudication Tool (OSAT) was developed by Telligen. The tool was customized to capture the data elements for Evaluation of Footwear and Neurological Evaluation performance measures. In addition to assisting the auditor with verification of age, diabetes mellitus, and history of bilateral foot/leg amputation, the tool provided the ability to capture location of documentation for each individual data element. Upon completion of abstraction at each on-site visit, the auditors performed back-up onto an encrypted flash drive. At the completion of the audit, the case results were exported from the tool and analyzed. No patient or physician identifiable information was captured. The tool provided the ability to enter data for a maximum of 100 cases per practice site.

OSAT was developed using the Product Designer Module. The module is used to compose abstraction resource files which define abstraction components. The module allows for unique project creation, while tailoring features to each customer's needs. Questions, answers, and measures are added as defined by the project. In addition, the tool is sophisticated enough to allow for the creation of skip, edit, and measure logic, based on the needs of the project. Skip logic defines rules for enabling questions based on defined patterns. Edit logic defines validations to be performed on answers provided by users of the tool. During the design phase, functionality tests were conducted with ongoing abstractor recommendations being incorporated into the application. Once the design functionality was complete, an OSAT build was created and tested to ensure readiness for field use.

1b.3 If no or limited performance data on the measure as specified is reported in 1b2

Table 1. Measure #126 (NQF 0417): Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy – Neurological Evaluation (Source Thomson Reuters Database)

CPT	Description	2011		2012	
		N	%	N	%
Denom	All continuously enrolled patients aged 18 years and older with a diagnosis of diabetes mellitus	907,810		798,722	
Num	Patients who had a lower extremity neurological exam performed at least once within 12 months	8,069	0.89%	9,771	1.08%
G8404	Lower Extremity Neurological Exam Performed	7,359	0.81%	8,978	0.99%
G8406	Lower Extremity Neurological Exam not Performed for Documented Reasons	129	0.01%	194	0.02%
G8405	Lower Extremity Neurological Exam not Performed	892	0.10%	942	0.10%

APPENDIX

2011 Reporting Experience
Including Trends (2008-2012)
Physician Quality Reporting System

Table A22. Eligible Professional (EP) Eligibility and Participation Information by Individual Measure for the Physician Quality Reporting System (2008 to 2011)

Measure Number	Measure Description	EPs in 2008	EPs in 2009	EPs in 2010	EPs in 2011	Reporting Rate in 2008	Reporting Rate in 2009	Reporting Rate in 2010	Reporting Rate in 2011
116	Antibiotic Treatment for Adults with Acute Bronchitis: Avoidance of Inappropriate Use	98,563	99,564	98,605	100,215	0.2%	0.3%	0.4%	0.4%
117	Diabetes Mellitus: Dilated Eye Exam in Diabetic Patient	320,355	326,026	340,041	347,761	2.3%	4.0%	4.3%	5.2%
118	Coronary Artery Disease (CAD): Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) Therapy for Patients with CAD and Diabetes and/or Left Ventricular Systolic Dysfunction (LVSD) ^{a,b}	215,770	222,374	1,751	2,266	0.7%	1.7%	100.0%	96.6%
119	Diabetes Mellitus: Urine Screening for Microalbumin or Medical Attention for Nephropathy in Diabetic Patients	321,407	311,093	325,839	332,508	1.5%	3.0%	3.1%	3.7%
121	Chronic Kidney Disease (CKD): Laboratory Testing (Calcium, Phosphorus, Intact Parathyroid Hormone (iPTH) and Lipid Profile)	37,451	46,392	53,494	61,611	0.7%	3.2%	4.4%	3.7%
122	Chronic Kidney Disease (CKD): Blood Pressure Management	37,452	46,295	53,335	61,449	1.2%	3.1%	4.3%	3.4%
123	Chronic Kidney Disease (CKD): Plan of Care – Elevated Hemoglobin for Patients Receiving Erythropoiesis-Stimulating Agents (ESA)	37,450	46,026	52,359	60,684	0.9%	1.6%	1.2%	0.9%
124	Health Information Technology (HIT): Adoption/Use of Electronic Health Records (EHR)	735,245	758,066	761,891	781,820	1.7%	5.0%	6.9%	9.1%
126	Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy – Neurological Evaluation	317,190	357,891	338,908	345,501	0.4%	0.8%	1.0%	1.4%
127	Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention – Evaluation of Footwear	317,155	357,851	338,907	345,497	0.2%	0.6%	0.7%	1.0%
128	Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up	732,278	782,405	704,404	722,617	0.3%	1.1%	1.3%	2.7%
130	Documentation and Verification of Current Medications in the Medical Record	265,808	768,837	691,221	710,120	0.7%	2.1%	3.4%	6.2%

Table A24. Eligible Professional (EP) Individual Measure Reporting Consistency Across Program Years for the Physician Quality Reporting System (2008 to 2011)

Measure Number	Measure Description	Participating EPs Reporting Individually 2008 to 2011 ^a	Participating EPs Reporting Individually 2009 to 2011 ^a	Participating EPs Reporting Individually 2010 to 2011 ^a	Participating EPs Reporting Individually 2011 Only ^a	Average Number of Years EPs Reported the Measure ^b	Standard Deviation for Average Number of Years EPs Reported the Measure ^b
119	Diabetes Mellitus: Urine Screening for Microalbumin or Medical Attention for Nephropathy in Diabetic Patients	1,476	2,416	2,484	5,414	2.00	1.08
121	Chronic Kidney Disease (CKD): Laboratory Testing (Calcium, Phosphorus, Intact Parathyroid Hormone (iPTH) and Lipid Profile)	94	540	783	827	1.96	0.88
122	Chronic Kidney Disease (CKD): Blood Pressure Management	128	518	628	795	1.99	0.94
123	Chronic Kidney Disease (CKD): Plan of Care – Elevated Hemoglobin for Patients Receiving Erythropoiesis-Stimulating Agents (ESA)	72	128	110	225	2.09	1.09
124	Health Information Technology (HIT): Adoption/Use of Electronic Health Records (EHR)	5,611	15,576	17,301	31,496	1.93	0.99
126	Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy – Neurological Evaluation	147	629	1,158	2,675	1.62	0.84
127	Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention – Evaluation of Footwear	83	488	669	2,230	1.55	0.82
128	Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up	754	2,160	3,024	13,380	1.50	0.84
130	Documentation and Verification of Current Medications in the Medical Record	730	6,334	9,564	26,706	1.56	0.80
131	Pain Assessment Prior to Initiation of Patient Therapy and Follow-Up	1,572	1,569	1,511	3,078	2.21	1.17
134	Screening for Clinical Depression and Follow-Up Plan	42	139	230	328	1.86	0.92
135	Chronic Kidney Disease (CKD): Influenza Immunization	n/a	55	30	176	1.54	0.82

Table A28. Percent of Eligible Professionals who Participated and had at Least a 90 Percent Performance Rate by Individual Measures for the Physician Quality Reporting System (2011)

Measure Number	Measure Description	Percent of Eligible Professionals Who Had a Performance Rate of At Least 90 Percent
100	Colorectal Cancer Resection Pathology Reporting: pT Category (Primary Tumor) and pN Category (Regional Lymph Nodes) with Histologic Grade	93.1%
102	Prostate Cancer: Avoidance of Overuse of Bone Scan for Staging Low-Risk Prostate Cancer Patients	55.6%
104	Prostate Cancer: Adjuvant Hormonal Therapy for High-Risk Prostate Cancer Patients	69.1%
105	Prostate Cancer: Three-Dimensional (3D) Radiotherapy	94.1%
106	Major Depressive Disorder (MDD): Diagnostic Evaluation	73.1%
107	Major Depressive Disorder (MDD): Suicide Risk Assessment	78.0%
108	Rheumatoid Arthritis (RA): Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy	55.7%
109	Osteoarthritis (OA): Function and Pain Assessment	69.4%
110	Preventive Care and Screening: Influenza Immunization for Patients \geq 50 Years Old	19.5%
111	Preventive Care and Screening: Pneumonia Vaccination for Patients 65 Years and Older	24.0%
112	Preventive Care and Screening: Screening Mammography	23.0%
113	Preventive Care and Screening: Colorectal Cancer Screening	24.7%
116	Antibiotic Treatment for Adults with Acute Bronchitis: Avoidance of Inappropriate Use	26.0%
117	Diabetes Mellitus: Dilated Eye Exam in Diabetic Patient	72.3%
118	Coronary Artery Disease (CAD): Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) Therapy for Patients with CAD and Diabetes and/or Left Ventricular Systolic Dysfunction (LVSD) ^{a,b}	28.1%
119	Diabetes Mellitus: Urine Screening for Microalbumin or Medical Attention for Nephropathy in Diabetic Patients	46.5%
121	Chronic Kidney Disease (CKD): Laboratory Testing (Calcium, Phosphorus, Intact Parathyroid Hormone (iPTH) and Lipid Profile)	31.0%
122	Chronic Kidney Disease (CKD): Blood Pressure Management	45.5%
123	Chronic Kidney Disease (CKD): Plan of Care - Elevated Hemoglobin for Patients Receiving Erythropoiesis-Stimulating Agents (ESA)	73.8%
124	Health Information Technology (HIT): Adoption/Use of Electronic Health Records (EHR)	98.5%
126	Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy – Neurological Evaluation	74.0%
127	Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention – Evaluation of Footwear	63.2%
128	Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up	33.7%

Table A13. Submission Information for Individual Measures Submitted through the Claims Mechanism for the Physician Quality Reporting System (2011)

Measure Number	Measure Description	Eligible Professionals	Eligible Professionals who Reported ≥ 1 Valid QDC	% of Eligible Professionals who Reported ≥ 1 Valid QDC	Eligible Professionals who Satisfactorily Reported	% of Eligible Professionals who Satisfactorily Reported	Average Reporting Rate per Eligible Professional
122	Chronic Kidney Disease (CKD): Blood Pressure Management	60,681	800	1.3%	376	47.0%	46.8%
123	Chronic Kidney Disease (CKD): Plan of Care - Elevated Hemoglobin for Patients Receiving Erythropoiesis - Stimulating Agents (ESA)	60,681	469	0.8%	201	42.9%	42.0%
124	Health Information Technology (HIT): Adoption/Use of Electronic Health Records (EHR)	779,813	45,845	5.9%	31,328	68.3%	59.9%
126	Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy – Neurological Evaluation	345,383	3,923	1.1%	1,837	46.8%	41.9%
127	Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention – Evaluation of Footwear	345,383	2,674	0.8%	1,027	38.4%	39.3%
128	Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up	721,678	11,529	1.6%	4,835	41.9%	35.7%
130	Documentation of Current Medications in the Medical Record	709,286	29,740	4.2%	17,761	59.7%	50.9%
131	Pain Assessment Prior to Initiation of Patient Therapy and Follow-Up	177,480	7,632	4.3%	5,979	78.3%	64.9%
134	Screening for Clinical Depression and Follow-Up Plan	120,626	744	0.6%	623	83.7%	74.3%
135	Chronic Kidney Disease (CKD): Influenza Immunization	45,120	155	0.3%	93	60.0%	52.1%
140	Age-Related Macular Degeneration (AMD): Counseling on Antioxidant Supplement	75,887	9,174	12.1%	6,186	67.4%	71.2%
141	Primary Open-Angle Glaucoma (POAG): Reduction of Intraocular Pressure (IOP) by 15% OR Documentation of a Plan of Care	45,599	5,226	11.5%	3,294	63.0%	63.5%
142	Osteoarthritis (OA): Assessment for Use of Anti-Inflammatory or Analgesic Over-the-Counter (OTC) Medications	218,838	1,899	0.9%	738	38.9%	38.4%

Table A23. Reporting and Performance Information by Individual Measure for the Physician Quality Reporting System (2008 to 2011)

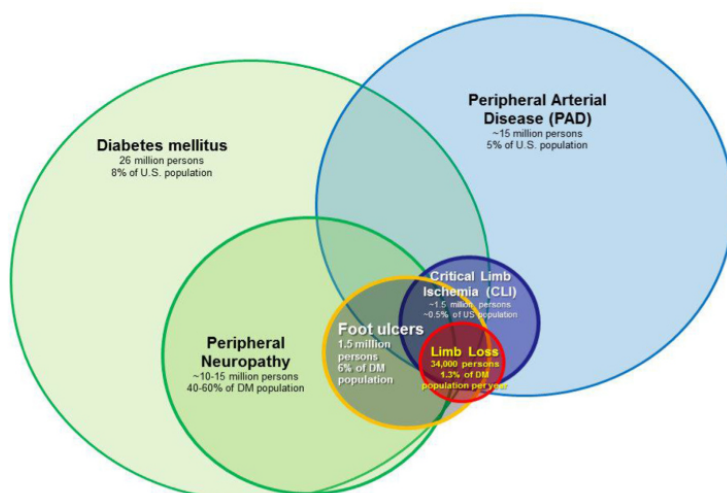
Measure Number	Measure Description	Average Percent of Instances Reported in 2008	Average Percent of Instances Reported in 2009	Average Percent of Instances Reported in 2010	Average Percent of Instances Reported in 2011	Average Performance Rate in 2008	Average Performance Rate in 2009	Average Performance Rate in 2010	Average Performance Rate in 2011
121	Chronic Kidney Disease (CKD): Laboratory Testing (Calcium, Phosphorus, Intact Parathyroid Hormone (iPTH) and Lipid Profile)	56.2%	84.7%	89.3%	87.1%	75.4%	35.2%	40.0%	45.3%
122	Chronic Kidney Disease (CKD): Blood Pressure Management	61.4%	78.9%	84.3%	80.1%	83.0%	68.9%	58.2%	65.6%
123	Chronic Kidney Disease (CKD): Plan of Care – Elevated Hemoglobin for Patients Receiving Erythropoiesis-Stimulating Agents (ESA)	56.0%	61.0%	54.1%	53.6%	82.0%	96.0%	94.8%	95.0%
124	Health Information Technology (HIT): Adoption/Use of Electronic Health Records (EHR)	65.3%	74.9%	78.5%	78.0%	100.0%	99.1%	99.2%	98.9%
126	Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy – Neurological Evaluation	58.3%	66.2%	59.5%	55.0%	63.0%	52.8%	74.2%	86.6%
127	Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention – Evaluation of Footwear	60.9%	67.3%	54.7%	53.3%	48.0%	43.9%	66.9%	69.2%
128	Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up	49.8%	54.5%	55.0%	65.5%	55.9%	49.6%	60.2%	58.3%
130	Documentation and Verification of Current Medications in the Medical Record	56.3%	69.9%	69.2%	70.5%	79.7%	68.4%	74.7%	85.7%
131	Pain Assessment Prior to Initiation of Patient Therapy and Follow-Up	63.1%	65.6%	73.5%	73.6%	98.1%	97.4%	97.3%	94.8%
134	Screening for Clinical Depression and Follow-Up Plan	54.4%	64.3%	73.0%	79.5%	83.4%	67.2%	84.2%	82.6%

Table A25. Individual Measure Performance Information Among Eligible Professionals who Participated Continuously in the Measure for Four Years for the Physician Quality Reporting System (2008 to 2011)

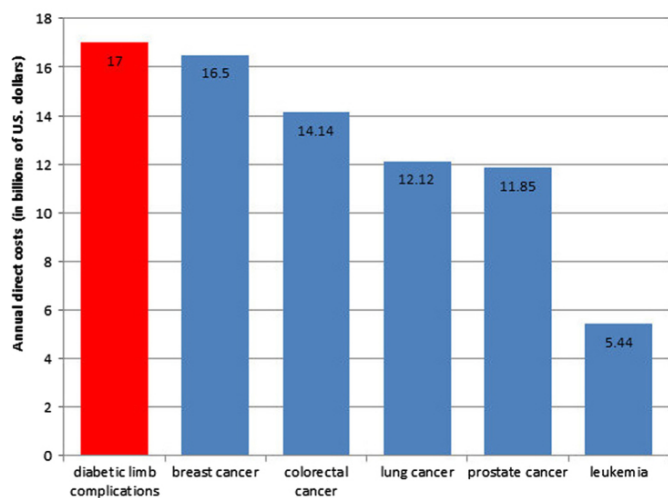
Measure Number	Measure Description	Eligible Professionals (EPs) who Reported the Measure Four Years Continuously*	Average Performance Rate per EP in 2008	Average Performance Rate per EP in 2009	Average Performance Rate per EP in 2010	Average Performance Rate per EP in 2011	Growth Rate
118	Coronary Artery Disease (CAD): Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) Therapy for Patients with CAD and Diabetes and/or Left Ventricular Systolic Dysfunction (LVSD) ^{ab}	71	87.5%	96.1%	83.2%	80.3%	-2.8%
119	Diabetes Mellitus: Urine Screening for Microalbumin or Medical Attention for Nephropathy in Diabetic Patients	1,476	69.0%	76.2%	79.8%	82.4%	6.1%
121	Chronic Kidney Disease (CKD): Laboratory Testing (Calcium, Phosphorus, Intact Parathyroid Hormone (PTH) and Lipid Profile)	94	89.9%	74.6%	72.0%	69.6%	-8.2%
122	Chronic Kidney Disease (CKD): Blood Pressure Management	128	88.4%	94.5%	94.3%	93.8%	2.0%
123	Chronic Kidney Disease (CKD): Plan of Care - Elevated Hemoglobin for Patients Receiving Erythropoiesis - Stimulating Agents (ESA)	72	81.9%	97.3%	98.0%	96.3%	5.5%
124	Health Information Technology (HIT): Adoption/Use of Electronic Health Records (EHR)	5,611	100.0%	99.9%	99.9%	99.4%	-0.2%
126	Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy – Neurological Evaluation	147	83.2%	89.0%	87.5%	88.9%	2.2%
127	Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention – Evaluation of Footwear	83	81.6%	79.1%	74.0%	82.9%	0.6%
128	Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up	754	55.8%	58.5%	62.7%	64.8%	5.1%
130	Documentation of Current Medications in the Medical Record	730	85.1%	83.2%	85.7%	88.5%	1.3%
131	Pain Assessment Prior to Initiation of Patient Therapy and Follow-Up	1,572	99.1%	98.8%	98.4%	97.7%	-0.5%

Appendix - 126 -

1c.3 Provide epidemiologic or resource use data that demonstrates the measure addresses a high priority aspect of healthcare).



Diabetes and subsequent foot complications affect incredibly high numbers of people. Ulcerations secondary to neuropathy and poor fitting footwear is a leading cause to infections, hospitalizations and amputations. The cost in both money and quality of life for the person with diabetes who develops an ulceration that leads to an amputation is staggering. The five year survival rate for a person with diabetes that undergoes an amputation is less than many forms of cancer.



The system of care for the diabetic foot: objectives, outcomes, and opportunities Neal R. Barshes, MD, MPH^{1*}, Meena Sigireddi, MPH², James S. Wrobel, DPM, MS³, Archana Mahankali, MD⁴, Jeffrey M. Robbins, DPM⁵, Panos Kougiyas, MD¹ and David G. Armstrong, DPM, MD, PhD⁶




4a.1 . For each CURRENT use, checked above, provide:

- Name of program and sponsor
- Purpose
- Geographic area and number and percentage of accountable entities and patients included

Quality Measures in Wound Care

US Wound Registry Measures for Reporting

<http://www.uswoundregistry.com/Specifications.aspx>

PQRS Measure #126, NQF #0417	Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy - Neurological Evaluation			
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5b.1. If this measure conceptually addresses both the same measure focus and the same target population as NQF-endorsed measure(s):

Describe why this measure is superior to competing measures (e.g., a more valid or efficient way to measure quality); OR provide a rationale for the additive value of endorsing an additional measure. (Provide analyses when possible.)

Here is NQF measure 0056 as used in PQRS from 2008-2013. Note report if any one of the three are performed. So data reported during this time would not necessarily reflect a neurological exam being performed—certainly brings into question are reliability for the measure as now being presented in 2014 in PQRS.

2012 Physician Quality Reporting System Measure Specifications Manual for Claims and Registry Reporting of Individual Measures

Measure #163: Diabetes Mellitus: Foot Exam

DESCRIPTION:

The percentage of patients aged 18 through 75 years with diabetes who had a foot examination

NUMERATOR:

Patients who received a foot exam (visual inspection, sensory exam with monofilament, or pulse exam)

Numerator Quality-Data Coding Options for Reporting Satisfactorily:

Foot Exam Performed

CPT II 2028F: Foot examination performed (includes examination through visual inspection, sensory exam with monofilament, and pulse exam – report when any of the three components are completed)

Measure #163 (NQF 0056): Diabetes: Foot Exam

2014 PQRS OPTIONS FOR INDIVIDUAL MEASURES: CLAIMS, REGISTRY

DENOMINATOR:

Patients 18 through 75 years of age who had a diagnosis of diabetes with a visit during the measurement period

NUMERATOR:

Patients who received a foot exam (i.e., visual inspection, sensory exam with monofilament **AND** pulse exam) during the measurement period

Numerator Quality-Data Coding Options for Reporting Satisfactorily:

Foot Exam Performed

G9226: Foot examination performed (includes examination through visual inspection, sensory exam with monofilament, and pulse exam – report when all of the 3 components are completed)

Significant change in measure for 2014, however, age range still exists excluding patients greater than 75 years of age.

Diabetic Foot & Ankle Care, Peripheral Neuropathy - Neurological Evaluation (NQF 0417)

EMeasure Name	Diabetic Foot & Ankle Care, Peripheral Neuropathy - Neurological Evaluation (NQF 0417)	EMeasure Id	1EAC3A7B-86CC-4F56-8B27-8D679DD1451C
Version number	1	Set Id	1677DD02-1AE2-4803-B32E-1EF8B4F23523
Available Date	No information	Measurement Period	January 1, 20xx through December 31, 20xx
Status	completed		
Author	Iowa Foundation for Medical Care		
Measure Steward	American Podiatric Medical Association		
Endorsed by	National Quality Forum		
Description	Percentage of patients aged 18 years and older with a diagnosis of diabetes mellitus who had a neurological examination of their lower extremities during one or more office visits within 12 months.		
Copyright			
Measure scoring	Proportion		
Measure type	Process		
Stratification	None		^
Risk Adjustment	None		^
Data Aggregation			
Rationale	Foot ulceration is the most common single precursor to lower extremity amputations among persons with diabetes. Treatment of infected foot wounds accounts for up to one-quarter of all inpatient hospital admissions for people with diabetes in the United States. Peripheral sensory neuropathy in the absence of perceived trauma is the primary factor leading to diabetic foot ulcerations. Approximately 45-60% of all diabetic ulcerations are purely neuropathic. Other forms of neuropathy may also play a role in foot ulcerations. Motor neuropathy resulting in anterior crural muscle atrophy or intrinsic muscle wasting can lead to foot deformities such as foot drop, equinus, and hammertoes. In people with diabetes, 22.8% have foot problems – such as amputations and numbness – compared with 10% of nondiabetics. Over the age of 40 years old, 30% of people with diabetes have loss of sensation in their feet.		
Clinical Recommendation Statement	Recognizing important risk factors and making a logical, treatment-oriented assessment of the diabetic foot requires consistent and thorough diagnostic approach using a common language. Without such a method, the practitioner is more likely to overlook vital information and to pay inordinate attention to less critical points in the evaluation. A useful examination will involve identification of key risk factors and assignment into appropriate risk category. Only then can an effective treatment plan be designed and implemented. (ACFAS/ACFAOM Clinical Practice Guidelines)		
Improvement notation	Higher score indicates better quality		^
Measurement duration	12 month(s)		^
Reference	Frykberg, RG; Armstrong, DG; Giurini, J; Edwards, A; Kravette, M; Kravitz, S; Ross, C; Stavosky, J; Stuck, R; and Vanore, J; Diabetic Foot Disorders: A Clinical Practice Guideline. Supplement to JFAS, 2000.		
Reference	Boulton AJM. Comprehensive Risk Examination and Foot Assessment. Diabetes Care. August 2008 31(8):1679-1685.		
Definition			
Guidance	At least two of the five components of the lower extremity neurological exam (reflexes, vibratory, proprioception, sharp/dull, and 5.07 filament detection) must be documented in order to meet the numerator requirements.		
	Categorization System: - Risk Category: 0 Risk Profile: Normal Evaluation Frequency: Annual - Risk Category: 1 Risk Profile: Peripheral Neuropathy (LOPS) Evaluation Frequency: Semi-Annual - Risk Category: 2 Risk Profile: Neuropathy, deformity, and/or PAD Evaluation Frequency: Quarterly - Risk Category: 3		

Risk Profile: Previous ulcer or amputation
Evaluation Frequency: Monthly to quarterly



Table of Contents

- [Population criteria](#)
- [Data criteria \(QDS Data Elements\)](#)
- [Summary Calculation](#)

Population criteria

- **Initial Patient Population =**
 - AND: "Patient characteristic: birth date" >= 18 year(s) starts before start of
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement" during "Measurement Period"
 - AND: "Diagnosis active: Diabetes" starts before or during
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement" during "Measurement Period"
- **Denominator=**
 - AND: "Initial Patient Population"
 - AND NOT:
 - AND:
 - OR: "Diagnosis active: Bilateral Amputee" starts before start of
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement" during "Measurement Period"
 - OR:
 - AND: "Physical exam finding not done: Patient Reason" for "Vibratory Sense Finding SNOMED-CT Code List"
 - AND: "Physical exam finding not done: Patient Reason" for "Patellar or Achilles Reflex Finding SNOMED-CT Code List"
 - AND: "Physical exam finding not done: Patient Reason" for "Proprioception Finding SNOMED-CT Code List"
 - AND: "Physical exam finding not done: Patient Reason" for "Sharp/Dull Sensation Finding SNOMED-CT Code List"
 - AND: "Physical exam finding not done: Patient Reason" for "Monofilament Detection Finding SNOMED-CT Code List"
 - during
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement" during "Measurement Period"
- **Numerator =**
 - OR:
 - AND:
 - OR: "Diagnosis active: Left Foot Amputee"
 - OR: "Diagnosis active: Left Lower Limb Amputee"
 - OR: "Diagnosis active: Lower Limb Amputee (laterality: 'left')"
 - starts before start of
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement" during "Measurement Period"
 - AND:
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'right foot')"
 - OR:

- AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'right foot')"
 - during
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement"
 - during "Measurement Period"
- OR:
 - AND:
 - OR: "Diagnosis active: Right Foot Amputee"
 - OR: "Diagnosis active: Right Lower Limb Amputee"
 - OR: "Diagnosis active: Lower Limb Amputee (laterality: 'right')"
 - starts before start of
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement"
 - during "Measurement Period"
 - AND:
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'left foot')"

- AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'left foot')"
 - during
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement"
 - during "Measurement Period"
- OR:
 - AND:
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'right foot')"
 - OR:
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'right foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'right foot')"
 - AND:
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Vibratory Sense Finding (anatomical location: 'left foot')"

- AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Patellar or Achilles Reflex Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Proprioception Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'left foot')"
 - OR:
 - AND: "Physical exam finding: Sharp/Dull Sensation Finding (anatomical location: 'left foot')"
 - AND: "Physical exam finding: Monofilament Detection Finding (anatomical location: 'left foot')"
 - during
 - OR: "Encounter: Inpatient or Ambulatory"
 - OR: "Procedure performed: skin or nail trim or debridement"
 - during "Measurement Period"
- **Exclusions =**
 - None

Data criteria (QDS Data Elements)

- "Diagnosis active: Bilateral Amputee" using "Bilateral Amputee ICD-10-CM Code List (2.16.840.1.113883.3.67.1.101.1.143)"
- "Diagnosis active: Diabetes" using "Diabetes Code List GROUPING (2.16.840.1.113883.3.67.1.101.1.393)"
- "Diagnosis active: Left Foot Amputee" using "Left Foot Amputee ICD-10-CM Code List (2.16.840.1.113883.3.67.1.101.1.144)"
- "Diagnosis active: Left Lower Limb Amputee" using "Left Lower Limb Amputee Code List GROUPING (2.16.840.1.113883.3.67.1.101.1.146)"
- "Diagnosis active: Lower Limb Amputee" using "Lower Limb Amputee SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.152)"
- "Diagnosis active: Right Foot Amputee" using "Right Foot Amputee ICD-10-CM Code List (2.16.840.1.113883.3.67.1.101.1.145)"
- "Diagnosis active: Right Lower Limb Amputee" using "Right Lower Limb Amputee Code List GROUPING (2.16.840.1.113883.3.67.1.101.1.149)"
- "Encounter: Inpatient or Ambulatory" using "Inpatient or Ambulatory Code List GROUPING (2.16.840.1.113883.3.67.1.101.1.133)"
- "Patient characteristic: birth date" using "birth date HL7 Code List (2.16.840.1.113883.3.67.1.101.1.24)"
- "Physical exam finding: Monofilament Detection Finding" using "Monofilament Detection Finding SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.407)"
- "Physical exam finding: Patellar or Achilles Reflex Finding" using "Patellar or Achilles Reflex Finding SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.404)"
- "Physical exam finding: Proprioception Finding" using "Proprioception Finding SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.405)"
- "Physical exam finding: Sharp/Dull Sensation Finding" using "Sharp/Dull Sensation Finding SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.406)"
- "Physical exam finding: Vibratory Sense Finding" using "Vibratory Sense Finding SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.403)"
- "Physical exam finding not done: Patient Reason" using "Patient Reason Code List GROUPING (2.16.840.1.113883.3.67.1.101.1.411)"
- "Procedure performed: skin or nail trim or debridement" using "skin or nail trim or debridement Code List GROUPING (2.16.840.1.113883.3.67.1.101.1.394)"
- Attribute: "Laterality: Left" using "Left SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.8901)"
- Attribute: "Laterality: Right" using "Right SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.8902)"
- Attribute: "Anatomical location: Left foot" using "Left foot SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.8903)"
- Attribute: "Anatomical location: Right foot" using "Right foot SNOMED-CT Code List (2.16.840.1.113883.3.67.1.101.1.8904)"

Summary Calculation

Calculation is generic to all measures:

- Calculate the final denominator by adding all that meet denominator criteria.
 - Subtract from the final denominator all that do not meet numerator criteria yet also meet exclusion criteria. Note some measures do not have exclusion criteria.
 - The performance calculation is based on the "Measure scoring" from header information above:
 - For "Proportion" measures, the calculation is the number meeting numerator criteria divided by the final denominator.
 - For "Ratio" and "Continuous Variable" measures, follow the calculation instructions in the Data Aggregation header information above, if present.
 - For measures with multiple denominators, repeat this process for each denominator and report each result separately.
 - For measures with multiple patient populations, repeat this process for each patient population and report each result separately.
 - For measures with multiple numerators, calculate each numerator separately within each population using the paired exclusion.
-

Review

QJM

Predicting foot ulcers in patients with diabetes: a systematic review and meta-analysis

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Summary

Clinical guidelines recommend that all patients with diabetes should be screened annually to establish their risk of foot ulceration. The aim of this systematic review was to quantify the predictive value of diagnostic tests, physical signs and elements from the patient's history in relation to diabetic foot ulcers. Observational studies were identified from: electronic databases (MEDLINE, EMBASE and CINAHL); bibliographies of studies meeting the inclusion criteria; review articles and clinical guidelines; direct contact with authors. Published reports of cohort and case-control studies were considered for inclusion. Pooled estimates were calculated from absolute numbers as weighted mean differences, standard mean differences or odds ratios. Adjusted odds ratios from published

reports were also extracted. We identified five case-control and 11 cohort studies. The incidence of foot ulcers ranged from 8% to 17% in the cohort studies, with varying lengths of follow-up. Diagnostic tests and physical signs that detect peripheral neuropathy (biothesiometry, monofilaments and absent ankle reflexes), and those that detect excessive plantar pressure (peak plantar pressure and joint deformity) were all significantly associated with future diabetic foot ulceration. However, there was a paucity of evidence concerning the predictive value of symptoms and signs. Further research is needed to establish the independent factors associated with diabetic foot ulceration, particularly elements from a patient's history and physical examination.

Introduction

The prevalence of foot ulceration among patients with diabetes mellitus ranges from 1.3% to 4.8% in the community, to as high as 12% in hospital.¹ This represents considerable patient morbidity, and is associated with substantial health-care costs. The pathophysiology of diabetic foot ulceration is multifactorial, but peripheral neuropathy is thought to be responsible for most cases.

To prevent foot ulceration and amputation, clinical guidelines recommend early identification of risk, based on annual foot screening of all

diabetic patients, with targeting of preventive and treatment interventions to 'high risk' individuals.^{2–4} Key to this preventive strategy is a structured clinical assessment that incorporates diagnostic tests alongside a thorough history and examination.

Current guidelines have not integrated data from primary studies that relate to the prognostic importance of diagnostic tests, physical signs and patient history (alone or in combination), the indicators that underlie any structured approach to preventive risk stratification in diabetic patients. We therefore

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undertook a systematic review to determine the predictive values of such features in estimating the risk of diabetic foot ulceration.

Methods

We followed recommended guidance concerning the conduct of systematic reviews.⁵

Search strategy

Electronic search strategies were used to identify studies which assessed the predictive value of diagnostic tests, signs and symptoms using MEDLINE (1966–February 2005), EMBASE (1980–March 2005), CINAHL1982–February 2005. The electronic search strategy was developed from clinical MeSH headings and text words. The search strategy is available from authors. We searched the bibliographies of included studies, review articles and national clinical guidelines.

Inclusion criteria

(i) Published reports of cohort or case-control studies that evaluated the factors used to predict diabetic foot ulceration. (ii) All study participants free of active foot ulceration at the time of study entry. (iii) All study participants in either study design had a diagnosis of diabetes (either type I or type II). The outcome (reference standard) was foot ulceration.

Definitions and explanations for the predictive factors assessed in the review are presented in Box 1.

Quality assessment

Assessment of methodological quality was used items adapted from the QUADAS tool, recommendations for methodological standards for clinical prediction rules and a checklist for assessment of the methodological quality both of randomized and non-randomized studies of health-care interventions.^{6–8} Quality assessment was done independently by two reviewers (FC, MI), and the results were used for descriptive purposes to provide an overall evaluation of the included studies. Disagreements were resolved by discussion, and information not available in the reports was sought from the corresponding authors of the primary study.

Data extraction

Data were extracted from the studies as absolute numbers and as means with SDs to permit the re-calculation of data as weighted or standardized mean differences and 95% CIs. Where data were

available, they were re-calculated as pooled estimates of the effect of the predictive factors. All odds ratios and risk ratios presented in the included studies were also extracted from the published reports.

Statistical analyses

Data from the two different study designs are presented separately. We only present estimates of effectiveness where there were two or more reports for individual predictive factors. A complete list of estimates of all predictive factors is available from the authors.

As the review focused on a single outcome (diabetic foot ulceration) groups of patients were categorized into those who ulcerated and those who did not. Continuous outcomes, expressed as means and SDs, were pooled as weighted mean differences (WMD). Peak plantar pressure was measured using different dynamic platform-based equipment systems, and consequently a standardized mean difference (SMD) was used to pool data. Tests for heterogeneity were performed, and where heterogeneity was evident, a random effects model was used.⁹

Findings are presented using the following structure for potential predictive factors; diagnostic tests, physical signs and patient history.

Results

Characteristics of included studies

After independent assessment by two reviewers, 16 studies were judged to have met all inclusion criteria (Figure 1), with disagreements being resolved by discussion. Details of the study population and aspects of diagnostic tests, physical signs and patient history are presented in Tables 1 and 2. Five studies used a case-control design,^{10–14} and eleven a cohort design,^{15–25} (Tables 1 and 2). A conference abstract of unpublished data was also identified by the search.²⁶

Data from nine studies were available to calculate pooled estimates.^{10–14,16–18,22} The incidence of foot ulceration developed by patients in cohort studies ranged from 8% to 17%, but with lengths of follow-up varying from 12 weeks to 4 years (Table 2).

Quality assessment (Tables 3 and 4)

Case-control studies

All five studies used statistical methods to adjust for confounding factors in the analysis (Table 1).^{10–14}

Box 1 Descriptions of the index tests used to predict those at risk of diabetic foot ulceration

Peak plantar pressures

Plantar pressure measurements are used to identify specific areas of high pressure under the foot. Several pieces of equipment exist to measure high plantar pressure, producing static or measurements from in-shoe or force plate systems, with outputs manifest as simple or highly sophisticated quantitative measures.³³

Vibration perception threshold

Vibration perception threshold can be measured using a biothesiometer or a neurothesiometer. These are hand-held mains or battery operated units with a rubber tractor that vibrates at 100Hz. A linear scale or digital display shows the applied voltage. Subjects are tested by gradually increasing the amplitude from zero and indicating when they feel vibration. Scale readings of >25 V are considered to be a positive test result (i.e. an absence of sensation).³⁴

Transcutaneous oxygen tension (TcPO₂)

TcPO₂ measures the amount of oxygen delivered to the skin. An electrode is attached to the dorsum of the foot, e.g. at the base of the second metatarsal. It has been suggested that a TcPO₂ level >30 mmHg is indicative of good blood flow in the lower limb.³⁵

HbA_{1c} (glycosylated haemoglobin)

HbA_{1c} is the most widely used measure of long term glycaemic control in diabetes, being produced by the non-enzymatic glycosylation of haemoglobin at a rate proportional to prevailing glucose concentration and the life span of the erythrocyte. Target HbA_{1c} is set at between 6.5% and 7.5%.³⁶

Fasting blood glucose

Diabetes mellitus is diagnosed on >7.0 mmol/l fasting blood glucose. If random blood glucose is >7.8 mmol/l, then FBG should be checked.³⁶

Ankle brachial index

Ankle-brachial pressure index (or ABI, ankle-arm index, AAI) is used to diagnose lower limb ischemia. It is calculated by dividing the recorded the systolic pressure taken at a pedal artery by the value taken at the brachial artery, and is expressed as a ratio. Average values are 0.98 to 1.31, <0.8 is indicative of ischaemia and <0.5 indicative of a pre-gangrenous state. The position of the patient will influence the pressure in the artery at the ankle; when standing the pressure in the ankle will be >1, if supine the reading should be 1.²⁷

Serum creatinine

Levels of serum creatinine >350 µmol/l (4.0 mg/dl) are indicative of chronic renal insufficiency.³⁶

Cutaneous sensation (Monofilaments)

Monofilaments are used to detect presence or absence of cutaneous pressure sensation. The filament is applied at 90° to the foot, with enough pressure to cause the filament to buckle. It should be held in place for 2 s. The 1st, 3rd and 5th metatarsal heads, the plantar aspect of great toe and the apex of third toe, in both feet should all be tested. The test result is positive (i.e. there is an absence of sensation) if the patient is able to feel fewer than eight sites with a monofilament (fewer than four sites if one foot has been amputated).³⁶

Tuning fork

The tuning fork assesses vibration perception threshold (VPT). Although tuning forks permit the detection of vibration, traditional tuning forks do not allow the measurement of the amplitude threshold at which vibration becomes perceptible. Some tuning forks can be calibrated to vibrate at a given frequency (Hz), and can be interpreted by a score on a scale of 0–8.³⁸

Visual acuity

Good eye sight is important for effective self foot care and the avoidance of harm. Visual acuity is usually measured by the Snellen test chart, and is defined as poor if worse than 20/40.³⁶

Lower limb oedema

Distension of the affected tissues can be caused by a disruption to the normal mechanism of fluid exchange.²⁷

Tendon reflexes

Tendon hammers are used to elicit tendon reflexes (jerks). The ankle reflex tests the integrity of the spinal reflex pathway (S1, S2). When the foot is held in a slightly dorsi-flexed position and the Achilles tendon tapped, the fore foot will gently plantar flex. The ankle reflex is recorded as present, or absent.³⁹

Limited ST joint motion

At the subtalar joint, two-thirds inversion to one third eversion is considered normal.³³

Limited 1st metatarsal motion

The expected range of motion (ROM) at the 1st metatarsal phalangeal joint is 70°.³³

In two studies, insufficient detail was given about the index tests to permit the presentation of data.^{12,13}

Cohort studies

Seven studies reported adjusted estimates for potential confounding factors (Table 2).^{15–17,19,21,22,25} Patients received treatment between the index tests and the outcome (assessment of foot ulceration) in all except one study.²³

Quantitative estimates concerning the predictive value of diagnostic tests, patient history, symptoms and signs

Unadjusted and adjusted estimates of effect of all predictive factors—diagnostic tests, physical signs

and patient history—are summarized in Table 5. Pooled estimates (weighted and standardized mean differences) concerning the predictive value of diagnostic tests (peak plantar pressures, vibration perception threshold and HbA_{1c}) and the duration of diabetes are presented in Figure 2.

Diagnostic tests

Peak plantar pressures (Figure 2a, Table 5)

Two case-control studies and four cohort studies measured peak plantar pressure, using four different dynamic measuring systems (Musgrave,¹⁰ F-scan,²² EMED^{12,18,21} and a pedobarograph^{20,24}). High plantar pressures constitute a risk of ulceration: SMD 0.98 N/cm² (95%CI 0.63–1.33)^{10,12} for case-control studies, and SMD 0.47 N/cm² (95%CI 0.24–0.70) for cohort studies.^{18,22}

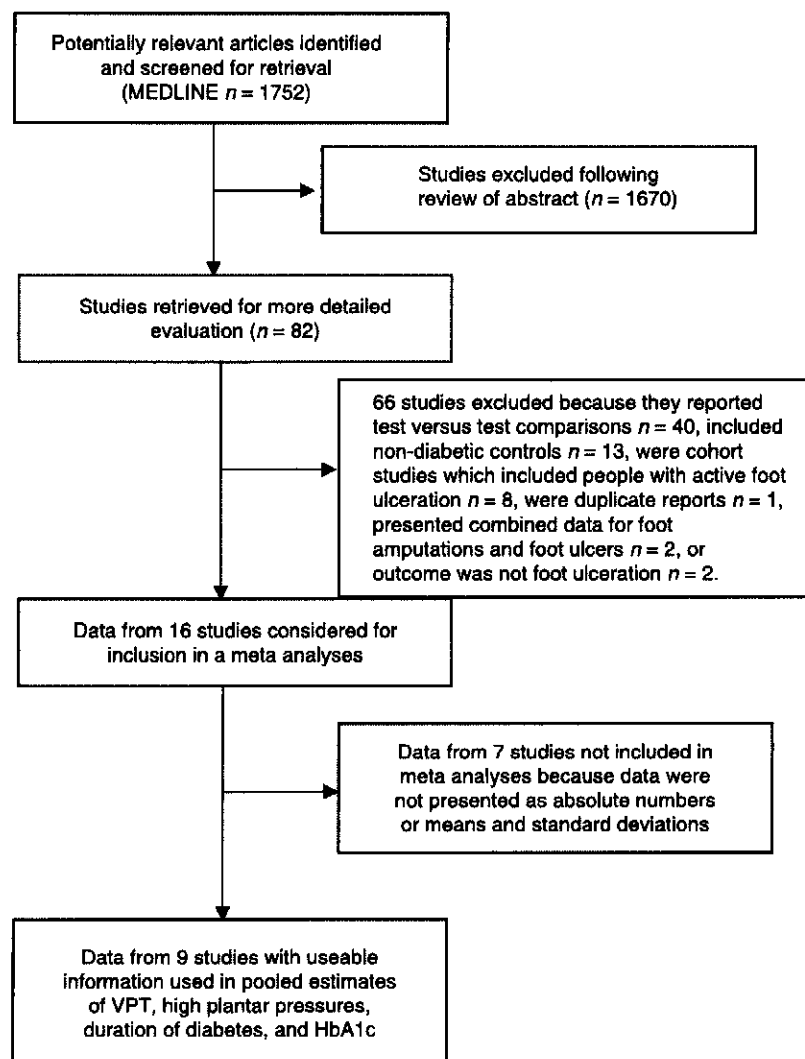


Figure 1. Flow diagram of studies in the review.

Table 1 Study interventions and outcomes: case-control studies

Author, year Study design, setting, and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)
Bennett, 1996 ¹⁰ Secondary care; diabetic units, Brisbane, Australia 27 cases, 50 controls	Peripheral nerve function assessed using two tests: biothesiometer; and Semmes-Weinstein monofilaments. Peripheral joint flexibility. Ankle joint dorsiflexion range of motion, measured with goniometer. Pressure of plantar aspect of foot, measured using a Musgrave Footprint system. Dynamic pressure recordings made of six foot prints with highest and lowest pressure prints discarded and average foot pressure obtained from the remaining four prints.	Age Sex Duration of diabetes Type of diabetes BMI HbA _{1c}	Not stated.
Boulton 1986 ¹¹ Secondary care diabetic foot clinic or emergency room, Miami Florida. 86 cases, 49 controls	VPT measured with a biothesiometer (three readings on each side). API was defined as ratio of posterior tibial artery systolic pressure to the brachial systolic pressures and values <0.8 were considered abnormal. Limited joint mobility	Age Duration of diabetes BMI HbA _{1c}	Foot ulcer was defined as an open lesion that was present below the level of the malleolus.
Lavery 1998 ¹² Texas diabetes institute, USA 76 cases, 149 controls	Peripheral sensory neuropathy assessed using vibration perception threshold testing at the distal great toe with a biothesiometer. Peripheral vascular disease of lower extremities evaluated using the Rose Intermittent Claudication Scale, the absence of palpable dorsalis pedis and posterior tibial pulses in the foot, transcutaneous oxygen tension on the dorsal aspect of the first intermetatarsal space (<30 mmHg), and the ankle-brachial systolic blood pressure index (<0.8). Three measurements of the first metatarsophalangeal joint, the subtalar joint, and ankle joint range of motion were averaged to assess limited joint mobility of the forefoot, rearfoot, and ankle.	Age Sex Duration of diabetes Diabetes type Education HbA _{1c} BMI Neuropathy Previous amputation Lower extremity bypass Tobacco use	Not stated.

Continued

Table 1 Continued

Author, year Study design, setting, and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)
McNeely 1995 ¹³ Veterans affairs medical centre USA 46 cases, 322 controls	Evaluation of foot for presence of hallux valgus, toe contractures, subluxation or dislocation of the metatarsophalangeal joints, and prominent metatarsal heads on the sole of the foot.	Alcohol abuse Intermittent claudication Retinopathy	
	EMED pressure platform system used to evaluate dynamic barefoot pressures on the sole of the foot. An average of pressures from three midgait steps was used for the purposes of analysis.		
	Distal vibratory sensation by vibrating 128 Hz tuning fork. If unable to perceive vibration at any of three sites on either foot, then vibratory sensation was considered absent.	% Men Age Caucasian	Foot ulcer graded as Seattle Wound Class 2.0 through 6.0.
	Aesthesiometry by Semmes-Weinstein monofilament on eight standardized plantar sites and one mid-dorsal site of each foot. Inability to perceive the 5.07 monofilament at any of the nine sites on either foot was classified as insensate.	BMI Married Education	
	Achilles tendon reflexes were graded as present or absent for each ankle.	Cigarette use Alcohol use	
	Ankle-arm BP index computed as the highest ankle (dorsalis pedis or posterior tibial) BP divided by the highest brachial BP (right or left) for each side.	Diabetes type Current diabetes	
	Cutaneous circulation by measuring transcutaneous oxygen tension on mid-dorsum of each foot.	treatment Duration of diabetes	
	For all variables measured bilaterally, the lower of the two readings (right or left) was used in the analysis.	Any formal diabetes education Random serum glucose Medical history	

Continued

Table 1 Continued

Author, year Study design, setting, and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)
Sriussadaporn 1997 ¹⁴ 55 cases, 110 controls	Ratio of ankle to brachial systolic BP of same side was calculated as ankle-brachial systolic index (ABI). Peripheral vascular insufficiency was diagnosed when ABI was <0.9. ABI of >1.2 suggested the presence of medial arterial calcification.	Sex	Foot ulcers defined as full-thickness disruption
		Marital status	of skin below mid-calf level with one or more of the more of the following features:
		Religion	duration of the ulcer >14 days, presence of severe infection, necrosis or gangrene.
	Peripheral nerve disorders were diagnosed on basis of short-latency somatosensory evoked potentials (SSEPs) following stimulation of the tibial nerve, recorded by Neuromatic 2000°C. Two questionnaires used to evaluate patients' knowledge of diabetes and foot-care behaviour.	Living area	
		Occupations	Diabetic patients in either group who had a past history of foot ulcer as defined by above criteria,
		Education	lower limb amputation, chronic venous ulcer, cerebrovascular disease, or spinal cord disease were not included in this study.
		Economic status	
		Smoking	
		Alcohol consumption	
		Diabetes duration	
		BMI	
		BP	
		Visual acuity	
		Diabetic knowledge score	
		Foot-care score	

Vibration perception threshold (VPT) (Figure 2b, Table 5)

Four case-control^{10–13} and six cohort studies^{16,17,20–22,25} found patients with foot ulcerations to have significantly higher VPT than those who did not: WMD 20.00 V (95%CI 11.81–28.20)^{10,12} for case-control studies and WMD 17.07 V (95%CI 13.89–20.26)^{17,22} for cohort studies.

Transcutaneous oxygen tension (Table 5)

Two case-control studies and one cohort study categorized patient measurements into groups

(≤30 mmHg and 31–60 mmHg). Transcutaneous pO₂ ≤30 mmHg was more strongly associated with the development of a foot ulcer, compared with pO₂ 31–60 mmHg.^{12,13,16}

HbA_{1c} (Figure 2c, Table 5)

In pooled results from four case-control studies, patients who developed foot ulcers had higher levels of HbA_{1c} than those who did not, but the effect did not reach statistical significance: WMD 0.95% (95%CI –0.33 to 2.23).^{10–12,14} Data from one cohort study did demonstrate a statistically significant effect: WMD 1.1% (95%CI 0.57–1.61).¹⁶

Table 2 Study interventions and outcomes: cohort studies

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Armstrong 2004 ¹⁵ Texas, USA Duration = mean follow-up 37.1 (12.3) weeks <i>n</i> = 100	Daily activity accelerometer/pedometer (measures the number of steps taken over a period of time, and records the time of day each step taken). VPT meter threshold >25 V defined as neuropathy	Age 68.5 (10) Sex 95.0 Duration of diabetes 13.7 (9.3) Foot risk category 68/32 BMI 30.0 (3.0)	Not stated	8/100 (8%).
Boyko 1999 ¹⁶ Ambulatory general internal medicine clinic patients at a veterans affairs medical centre Seattle, USA Duration not reported <i>n</i> = 900	Sensory testing performed at nine locations on each foot using Semmes-Weinstein monofilament. Inability to detect 10 g monofilament. Vibration sensation measured using a 128 Hz tuning fork. VPT graded present/absent. Cardiovascular autonomic neuropathy: mean heart rate variability on a continuous electrocardiogram, and immediate systolic BP response to standing from a supine position. Lower-limb transcutaneous O ₂ tension with TCM-3 monitors. TC PO ₂ flow measure in perfusion units Laser Doppler flowmetry on dorsal foot. Standard Doppler techniques for brachial and lower-limb arterial BP. BP measured in mmHg. Hallux BP measured using a penile cuff and hand-held Doppler. Random blood sample for plasma glucose (glucose oxidase method), serum creatinine and erythrocyte sedimentation rate.	Weight Height Diabetes duration Type 2 diabetes Insulin use Random glucose HbA _{1c} Erythrocyte sedimentation rate Serum creatinine TcPO ₂ dorsal foot Claudication <1 block Peripheral vascular disease. History of laser photocoagulation treatment Vision <20/40 History of ulceration Previous amputation Foot numbness and pain	Foot ulcer was defined as a full-thickness skin defect that required >14 days to heal. Outcome was defined as the first ulcer occurrence on the foot. Follow-up on both limbs was terminated when the first ulcer occurred on either during the follow-up period.	162 ulcers developed over 5442.6 cumulative person-years (3.0/100 person-years).

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Kastenbauer 2001 ¹⁷ Diabetes centre at the third medical department, Hospital Lainz, Vienna, Austria Duration = 4 years <i>n</i> = 187	X-ray taken of both feet to assess bone deformities and calcification of the media. Questionnaire for evaluating symptoms of peripheral neuropathy. Peripheral nerve conduction velocity, cardiorespiratory reflexes and orthostatic drop of systolic BP measured. PVD determined using palpability of foot pulses and ankle-arm index. VPT measured using a biothesiometer three times at the pulp of both great toes. Perception of 10 g monofilament tested at eight plantar sites on each foot: insensate to 2/8 regarded as abnormal.	Sex Age Diabetes duration Insulin use HbA _{1c} Serum creatinine Body weight BMI History of MI History of angiography Smoking Daily alcohol intake	Foot ulcers defined as full-thickness neuropathic plantar or lateral forefoot ulcerations penetrating the cutis and subcutis.	18 forefoot ulcerations in 10 patients out of a total of 187 patients.
Lavery 2003 ¹⁸ In-patient and out-patient clinics in Texas, USA Duration = 2 years <i>n</i> = 1666	Lower extremity sensory examination using 10 g Semmes-Weinstein monofilament. Abnormality defined as inability to detect 10 sites evaluated with monofilament on each foot VPT using biothesiometer, abnormal reading >25 V. Lower-extremity vascular status assessed by palpating dorsalis pedis and posterior tibial pulses. Peak foot pressures assessed using Novel EMED force-plate gait analysis system.	Age %Male Weight Duration of diabetes	Not stated.	263 patients (15.8%) developed an ulcer during 24 months follow-up.

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Litzelman 1997 ¹⁹ Primary care, Indiana USA. Duration = 1 year n = 352	Lower-extremity oedema assessed by pressing thumb over pretibial area for 5 s. Sensortek Thermal Sensitivity Testing apparatus and Semmes-Weinstein monofilament used as objective measures of neuropathy. Thermal sensation was defined as abnormal if detection of temperature change from a reference of 25°C was >2 SDs from the mean sensitivity threshold for a group of healthy people without diabetes. Touch pressure sensation tested with a single 10 g Semmes-Weinstein monofilament. Abnormal pressure anaesthesiometry, defined as the absence of sensation at one or more of three sites tested on the plantar surface of each foot.	Race %Women Age Annual income <\$10 000 Education level (years) BMI Duration of diabetes Taking insulin Taking oral hypoglycaemic agents.	Response variable was the existence of any foot wound at time of follow-up assessment. Rated using the Seattle Wound Classification System, which ranges from a grade 1.1, signifying absence of lesions, to grade 10, where the entire foot or leg is gangrenous. Outcome was then dichotomized and separately analysed at two thresholds of severity.	63/704 (8.9%)
Murray 1996 ²⁰ Secondary care diabetes centre and Manchester Foot Hospital, UK Duration = not reported n = 63	Neuropathy deficit score: sensations of pain, light touch, vibration and cold tested in both lower limbs and scored to the level up to which sensation was impaired. VPT measured at both great toes by biothesiometer and compared with age-matched 'normal' measurements. Mean of three measurements used for each great toe. Foot pressures measured using a dynamic optical pedobarograph.	Male Age Type 1 DM Duration of diabetes History of intrinsic ulcers	Ulcers were classed as intrinsic if they occurred on the plantar surface of the foot and were not associated with external trauma, extrinsic if they occurred as a result of shoe pressure or trauma (typically dorsal). Only intrinsic ulcers were considered in the analysis.	Seven intrinsic plantar ulcers documented in six patients. Total of 63 patients in study.

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
<i>n</i> = 248	Vibration perception threshold measured using a biothesiometer. 8 SWF monofilaments (1g to 100 g) used at the plantar aspect of the hallux. Maximal plantar foot pressure. F scan mat system, measuring dynamic pressure. Peripheral vascular disease (PVD) based on absent foot pulses.	History of foot amputation Type of diabetes		
Rith-Najarian 1992 ²³ Primary care, Minnesota, USA Duration = 3 years <i>n</i> = 358	Sensation status determined by applying the 5.07 monofilament to eight points on the plantar surface of each foot at time A or time B when the patient was blinded. Patients who failed to perceive the monofilament on one or more areas of either foot were retested twice before they were classified as insensate. Subset of patients had AAI calculated from measurements of right brachial artery and both posterior tibial arteries, obtained with a mercury manometer and a 2 MHz portable Doppler.	Age Duration of diabetes Sex	Ulcerations were defined as any full thickness penetration of the dermis on the plantar aspect of the foot.	41 ulcers from 358 patients (11.5%)
Veves 1992 ²⁴ Secondary care; clinics at diabetes centre, Manchester, UK. Duration = 30 months <i>n</i> = 86	Neuropathy deficit score (NDS) used to diagnose neuropathy, based on reduced or absent ankle reflexes and reduced or absent sensation to pain, touch and vibration. Foot pressures measured by optical pedobarography. Peak pressures >12.3 kg/cm ² considered abnormal. VPT measured at the great toe by biothesiometry. Upper threshold of normality was taken from established data based on measurements of a large number of healthy subjects.	Age Gender Diabetes type Duration of diabetes	Ulcers were classified as plantar when they occurred on plantar surface of foot and as dorsal if they occurred anywhere else on the foot.	15/86 with plantar ulceration and high pressures at baseline (17.4%)

Continued

Table 2 Continued

Author, year Study setting, duration and sample size	Diagnostic tests (with thresholds if appropriate)	Signs, symptoms and other risk factors	Definition of ulceration (outcome)	Incidence of ulceration
Young 1994 ²⁵ Secondary care, diabetes centre and foot clinic Manchester, UK Duration = 4 years <i>n</i> = 469	VPT was assessed by biothesiometry. Mean of three readings used to derive the value for each foot.	Sex Age Diabetes type Duration of diabetes HbA _{1c} Creatinine	Not stated.	First ulcers = 8/469 patients (10.2%)

Ankle brachial indices (ABI) (Table 5)

Four cohort^{16,17,21,23} and four case control studies^{11–14} measured blood pressure at the ankle and arm. Only one cohort study found an effect which remained evident after an adjustment for confounding.¹⁶

Fasting blood glucose and serum creatinine (Table 5)

There was inconsistent evidence that increasing levels of blood sugar (mmol/l)^{14,19} and creatinine (μmol/l) were associated with increased risk of ulceration.^{16,19}

Physical signs*Cutaneous sensation (monofilaments) (Table 5)*

One case-control study and five cohort studies all found statistically significant differences in the rate of foot ulceration between people whose feet were insensate to ≤5.07 monofilaments (≤10 g pressure) and those who were not, with ORs ranging from 2 to 10.^{13,16,19,21–23}

Absent ankle reflexes (Table 5)

Absent ankle reflexes were predictive of a higher risk of foot ulceration in one case-control¹³ and one cohort study,¹⁶ with unadjusted ORs of 4.9 and 1.4, respectively.

Visual acuity (Table 5)

Patients with lower mean visual acuity were at greater risk of foot ulceration in one case-control and one cohort study (adjusted RR 1.9).^{14,16}

Patient history*Duration of diabetes (Figure 2d, Table 5)*

In five case-control studies, patients who developed foot ulcers had diabetes for longer than those who did not, but this effect was not statistically significant: WMD 2.62 (95%CI –0.75 to 5.99).^{10–14} Combined data from two cohort studies did find a statistically significant effect: WMD 1.88 (95%CI 0.48–3.28).^{16,22}

History of foot ulceration, amputation and history of lower limb bypass (Table 5)

In four cohort studies investigating the risk associated with a history of foot ulceration,^{16,20–22} patients who had previous ulceration were more likely to develop diabetic foot ulcers (adjusted ORs ranging from 1.6 to 4.2). One case-control study and one cohort study found a history of amputation to be a risk factor for foot ulceration.^{12,16} These two studies also found that a history of lower limb bypass operation predicted future foot ulceration.

Discussion**Summary of findings**

We found evidence to support the use of diagnostic tests and physical signs that detect peripheral neuropathy, the principal cause of diabetic foot ulceration. High vibration perception thresholds (VPTs) using a biothesiometer or a tuning fork, high plantar pressure and 10 g monofilaments appear reliable methods to identify

Table 3 Case-control studies: quality assessment

Authors...	Bennett 1996 ¹⁰	Boulton 1986 ¹¹	Lavery 1998 ¹²	McNeeley 1995 ¹³	Sriussadaporn 1997 ¹⁴
Hypothesis clearly defined?	Y	Y	Y	Y	Y
Patient characteristics clearly described?	Y	Y	Y	Y	Y
Predictive factors clearly described?	Y	Y	Y	Y	Y
Main outcome measure defined?	Y	Y	Y	Y	Y
Patients selected consecutively?	NC	NC	Y	Y	NC
Patients representative of those who receive the test in practice?	Y	Y	Y	Y	Y
Context representative of the treatment majority of patients receive?	Y	Y	Y	Y	Y
Index tests (PF) reproducible?	Y	N	N	N	Y
Adjustment made for confounders?	Y	Y	Y	Y	Y
Same clinical data available when test results (PF) interpreted?	Y	Y	Y	Y	Y
Assessment of outcome blind to the results of the index test (PF)?	NA	NA	Y	NA	NA
Uninterpretable/intermediate test results (PF) reported?	N	N	NA	N	N
Sample size adequate for number of outcome events?	Y	Y	Y	Y	Y
Statistical tests for main outcomes adequate?	Y	Y	Y	Y	Y
Study sought to measure and report adverse events?	N	N	N	N	N

those at risk of future ulceration. Absent ankle reflexes, and limited joint motion at both the first metatarsal-phalangeal joint and the subtalar joint were also found to increase the risk of foot ulceration. These findings were evident across different study designs, pooled, unadjusted and adjusted estimates of effect. Established vascular disease, in the form of a history of previous amputation, ulceration or lower limb bypass procedures, was also consistently associated with risk of future ulceration.

None of the published studies reported on the predictive value of signs associated with foot trauma, such as inappropriate footwear and improperly cut toenails.

Evidence concerning the predictive value of 'contributory' factors in diabetic foot ulceration, such as some physical signs and elements from the patient's history, was less clear. For example, HbA_{1c} and ankle brachial indices (ABI, ABPI, or AAI) produced inconsistent and contradictory findings (Table 5). The length of time that a person had diabetes was marginally predictive in two cohort studies,^{16,22} although in five methodologically weaker case-control studies, the association was not statistically significant.¹⁰⁻¹⁴

Shortcomings of this review

Synthesized evidence from this review does support the predictive value of most conventional diagnostic tests used to assess the risk of foot ulceration in people with diabetes. However, only a minority of primary studies assessed the independent predictive value of diagnostic tests in addition to physical signs and elements from a patient's history. Furthermore, different cut-points have been used for many of the diagnostic tests, making comparisons between studies difficult. Some diagnostic tests require a standardized procedure when being carried out. For example, ankle brachial index studies (ABI, ABPI, or AAI) were difficult to interpret because of the lack of detail disclosed as to the position of the patient when blood pressure was measured. Ankle systolic pressure is affected by posture; 1 mmHg higher for each inch the ankle is below the heart.²⁷ This detail was missing from three case-control and four cohort studies, and prevented us from pooling data. Only one cohort study found <0.8 ABI to be predictive of future ulcer risk.¹⁶ The value of this procedure in that ulceration risk assessment is yet to be established.

Table 4 Cohort studies: quality assessment

Authors...	Armstrong 2004 ¹⁵	Boyko 1999 ¹⁶	Kastenbauer 2001 ¹⁷	Lavery 2003 ¹⁸	Litzelman 1997 ¹⁹	Murray 1996 ²⁰	Peters 2001 ²¹	Pham 2000 ²²	Rith-Najarian 1992 ²³	Veves 1992 ²⁴	Young 1994 ²⁵
Hypothesis clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Patient characteristics clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Predictive factors clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Main outcome measure defined?	Y	Y	Y	N	Y	Y	Y	N	Y	N	N
Patients selected consecutively?	Y	Y	Y	Y	Y	NC	Y	Y	Y	N	Y
Patients representative of those who receive the test in practice?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Whole sample or random selection of the sample's outcome verified?	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y
Characteristics of the patients lost to follow-up described?	NA	N	N	NA	N	NC	N	N	N	Y	NA
Context representative of the treatment majority of patients receive?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Index tests (PF) reproducible?	Y	N	N	Y	Y	Y	N	Y	N	Y	Y
Treatment given between index tests and outcome?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Adjustment made for confounders?	N	Y	N	NC	Y	N	N	Y	N	N	Y
Length of follow-up the same for all participants?	Y	N	N	Y	Y	N	N	N	N	N	NC
Same clinical data available when test results (PF) interpreted?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Assessment of outcome blind to the results of the index test (PF)?	NC	NA	Y	NA	NC	N	N	Y	N	N	NC
Uninterpretable/intermediate test results (PF) reported?	N	N	N	N	N	N	NC	N	N	N	NC
Withdrawals for the study explained?	NA	N	Y	NA	N	NA	NC	Y	N	Y	NA
Sample size adequate for number of outcome events?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Statistical tests for main outcomes adequate?	N	Y	Y	Y	Y	N	N	Y	N	N	Y
Study sought to measure and report adverse events?	N	N	N	N	N	N	N	N	N	N	N

Table 5 Summary of pooled estimates for predictive value of diagnostic tests, physical signs and patient history in relation to diabetic foot ulceration

	Pooled estimates WMD/SMD (95%CI)		Unadjusted risk/OR (95%CI)		Adjusted risk/OR (95%CI)	
	Case-control	Cohort	Case-control	Cohort**	Case-control	Cohort**
Diagnostic tests						
Peak plantar pressure ^{10,12,17,18,20,22} (kg/cm ² or N/cm ²)	SMD 0.98 (0.63–1.33) ^{10,12}	SMD 0.47 (0.24–0.70) ^{18,20}	3.6 (p<0.001) ¹²	3.2 (2.0–5.1) ²²	4.8 kg/cm ² (1.44–16.3) ¹⁰	6.3 (1.2–32.7) ¹⁷
Vibration perception threshold ^{10–13,16,17,22,25}	WMD 20.00 (11.81–28.20) ^{10,12}	WMD 17.07 (13.89–20.26) ^{17,22}	10.77 (4.59–25.73) ¹¹	8.2 (7.4–18.4) ²²	4.9 (1.0–24.0) ¹⁰	2 (1.4–2.9) ¹⁸ 2.0 kg/cm ² (1.2–3.3) ²² 25.4 (3.1–205) ¹⁷
Transcutaneous oxygen tension <30 mmHg ^{12,13,18}	–	–	1.1 (p=0.85) ¹²	1.35 (1.18–1.56) ¹⁶	57.87 (5.08–658.9) ¹³	1.25 (1.08–1.45) ¹⁶
HbA _{1c} ^{10–12,14–16,19}	0.95 (–0.33 to 2.23) ^{10,11,12,14}	1 (0.46–1.5) ¹⁶	26.9 (3.03–218.99) ¹³	1.26 (1.11–1.43) ¹⁶	1.69 (0.96 to 2.99) ¹⁰	–
Fasting blood glucose ^{14,19} (mmol increase)	–	–	2.99 (0.49–8.99) ¹⁴	1.08 (0.94–1.24) ¹⁹	3.2 (p<0.03) ¹²	–
Ankle brachial index ^{11,13,16}	–	–	1.16 (0.40–3.33) ¹³	1.25 (1.05–1.47) ¹⁶	–	1.20 (1.04–1.37) ¹⁶
			2.84 (p=0.08) ¹¹			

Serum creatinine ^{15,19}	-	-	1.16 (1.04-1.29)* ¹⁶	-	-
Physical signs					
Monofilament (SWF) ^{13,16,19,21-23}	-	-	9.99 (3.50-28.49) ¹³	-	2.17 (52-3.08)* ¹⁷
			3.37 (2.45-4.63)* ¹⁶		5.23 (2.26-12.13) ¹⁹
			5.46 (2.39-12.45) ¹⁹		33.2 (5.6-181.6) ²¹
			5.4 (2.6-11.6) ²²		2.4 (1.1-5.3) ²²
			9.9 (4.8-21.0) ²⁴		1.93 (1.42-2.63)* ¹⁶
Visual acuity <20/20 ¹⁴ (<20/40) ¹⁶	-	-	-	0.223 per unit decrease in decimal visual acuity (0.005-0.39) ¹⁴	-
			2.31 (1.72-3.09)* ¹⁶		
Lower limb oedema ^{16,19}	-	-	-	-	-
			1.52 (1.12-2.06)* ¹⁶		
			0.88 (0.37-2.10) ¹⁹		
Absent reflexes ^{13,16}	-	-	4.58 (2.11-9.94) ¹³	6.48 (2.37-18.06) ¹³	-
Limited subtalar joint motion ^{12,22}	-	-	2.1 (p<0.009) ¹²	-	-
			1.40 (1.03-1.90)* ¹⁶		
(ROM degrees)			1.03 (1.00-1.05) ²²		
Limited 1st metatarsal-phalangeal motion ^{11,12,16,22}	-	-	3.57 (1.71-7.46) ¹¹	-	-
			1.30 (1.11-1.54)* ¹⁶		
(ROM degrees)			1.05 (1.01-1.03) ²²		
Patient history					
Gender ^{12,22}	-	-	5.7 (p<0.001) ¹²	2.7 (p<0.05) ¹²	-
			2.27 (1.43-3.70) ²²	1.0 (0.97-1.06) ¹⁰	-
Duration of diabetes ^{10-14,16,22}	2.62 (-0.75 to 5.99) ¹⁰⁻¹⁴	1.0 (0.57-1.62) ¹⁶	-	3.0 (<0.04) ¹²	-

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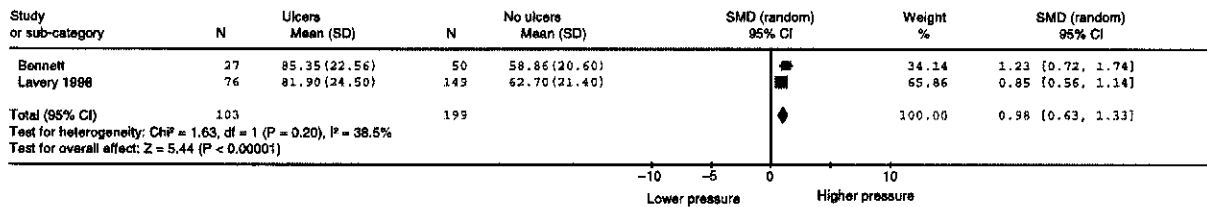
Table 5 Continued

	Pooled estimates WMD/SMD (95%CI)		Unadjusted risk/OR (95%CI)		Adjusted risk/OR (95%CI)	
	Case-control	Cohort	Case-control	Cohort**	Case-control	Cohort**
Alcohol use ^{12,17}	–	–	1.8 (<i>p</i> = 0.19) ¹²	–	–	5.1 (1.1–24.0)* ¹⁷
Previous ulceration ^{16,20–22}	–	–	–	2.46 (1.84–3.29)* ¹⁶	–	1.63 (1.17–2.26)* ¹⁶
				5.11 (3.17–8.24) ²²		4.2 (1.1–16.7) ²¹
Previous amputation ^{12,16}	–	–	40.5 (<i>p</i> < 0.001) ¹²	56.8 (13.4–241.2)* ²⁰	10.0 (<i>p</i> < 0.02) ¹²	2.81 (1.84–4.29)* ¹⁶
Lower limb bypass ^{12,16}	–	–	3.0 (<i>p</i> < 0.04) ¹²	2.51 (1.53–4.10)* ¹⁶		–

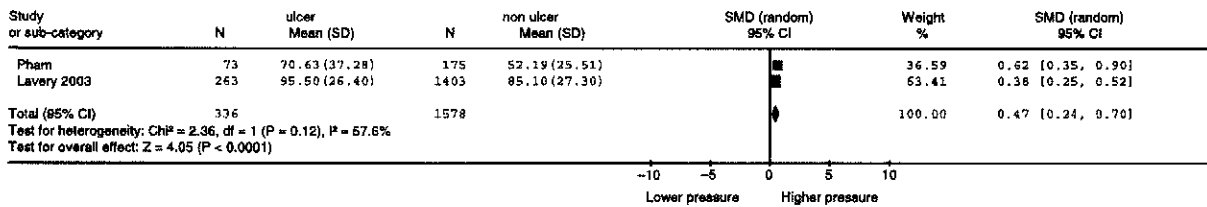
*Data reported as relative risk rather than odds ratio in these cohort studies. **Reciprocal of relative risk reported in some cohort studies, so that reference category remained consistent for all comparisons. WMD, weighted mean differences; SMD, standardized mean differences; –, pooled estimate not calculated.

a

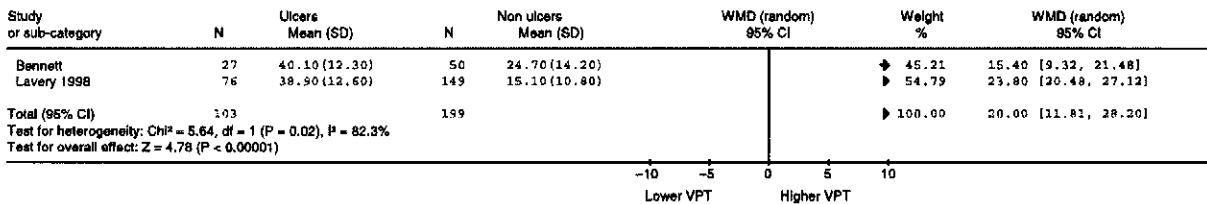
Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
 Comparison: 01 Peak Plantar Pressure (N/cm²)
 Outcome: 01 Case control studies



Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
 Comparison: 01 Peak Plantar Pressure (N/cm²)
 Outcome: 02 Cohort studies

**b**

Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
 Comparison: 02 Vibration perception threshold (Volts)
 Outcome: 01 Case control studies



Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
 Comparison: 02 Vibration perception threshold (Volts)
 Outcome: 02 Cohort studies

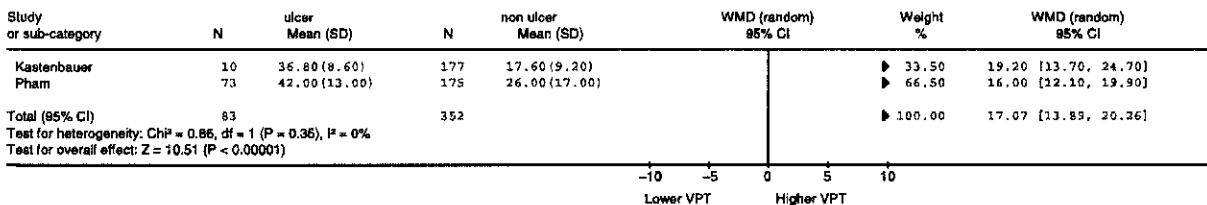


Figure 2. Forest plots of pooled data for the predictive value of **a** peak plantar pressure, **b** vibration perception threshold, **c** HbA_{1c} and **d** duration of diabetes, for foot ulceration in diabetes. Continues overleaf.

The review included studies that assessed multiple potential predictive factors, and there is a risk of false positive findings in the estimates reported from the primary studies.²⁸ The pooled estimates of nearly all predictive factors showed evidence of significant heterogeneity. This is a consequence of the different and varied definitions for some of the predictive factors, that different cut-points were used, different methods with ascertaining diabetic ulceration and different lengths of follow-up (Tables 1 and 2). Standardizing diagnostic tests and

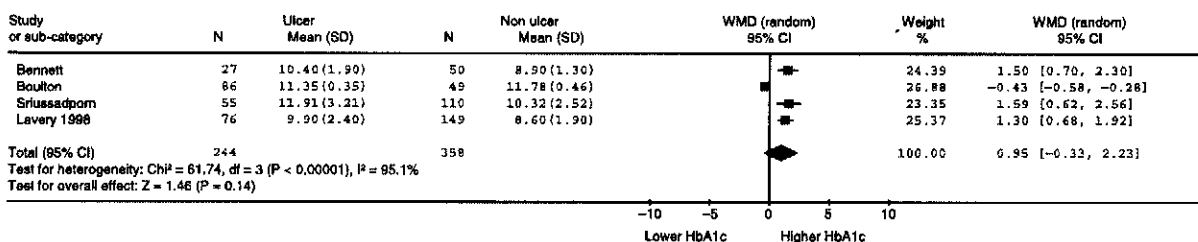
the cut-offs used would be helpful for both research and practice.

Context of other studies

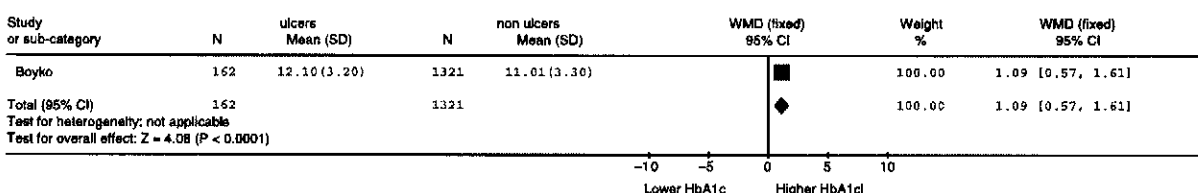
A previous systematic review assessing some of the methods advocated for preventing diabetic foot ulceration suggested that monofilaments, biothesiometer, tuning fork and peak plantar pressure were useful screening tests.²⁹ Our results are

C

Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
 Comparison: 03 HbA1c (%)
 Outcome: 01 Case control studies

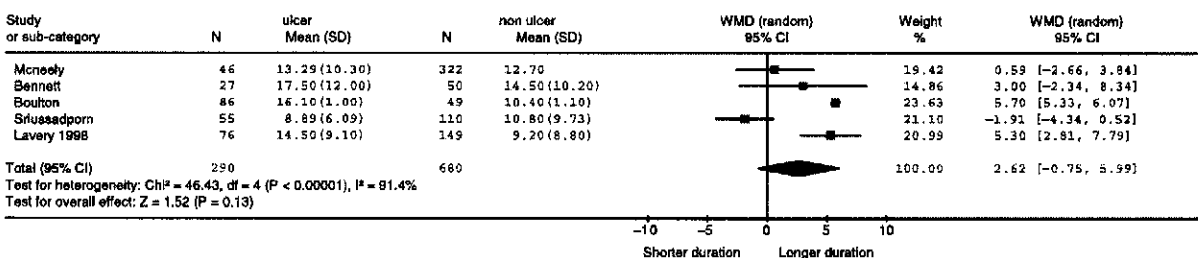


Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
 Comparison: 03 HbA1c (%)
 Outcome: 02 Cohort studies



d

Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
 Comparison: 04 Duration of diabetes (years)
 Outcome: 01 Case control



Review: Predictive factors for the assessment of people with diabetes who are at risk of foot ulceration
 Comparison: 04 Duration of diabetes (years)
 Outcome: 02 Cohort

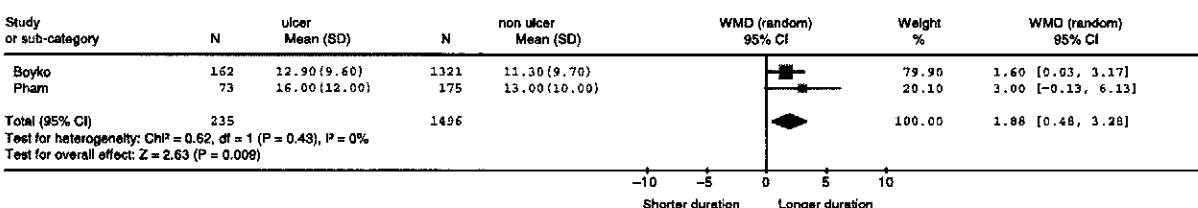


Figure 2. Continued.

consistent with these findings. We also identified eight additional studies that have provided more evidence of the predictive value of tests, and a more integrated approach has permitted data to be pooled.

National and international clinical guidelines also suggest that previous foot amputation and foot ulceration are useful criteria for the identification of patients at 'high risk' of foot ulceration.²⁻⁴ These guidelines are supported by the findings from this systematic review. However, some

recommendations in clinical guidelines do not appear to be based on any firm evidence. For example, we could find no convincing data to support that 'absent leg or pedal pulses' is a risk factor for diabetic foot ulceration, despite the suggestion that this clinical sign is a key indicator of risk.^{3,4} Few studies adopted a comprehensive approach to the evaluation of predictive factors, and some variables that could predispose to foot ulceration, such as levels of exercise, the presence of callus, Charcot deformity or adequate footwear,

have not been subject to extensive evaluation. There is a clear need for further research to address these clinical uncertainties.

Generalizability of findings

The incidence of foot ulcerations in the cohort studies varied from 8% to 17% (Table 2). These are much higher levels of ulceration than those cited in UK national clinical guidelines (5–7%), diabetes text books (7%) and in a national survey (5%).^{3,4,30,31} This observed difference in incidence may imply that patients included in the studies had more severe disease than those in the general diabetic population. Most of these patients were recruited from hospital diabetes clinics and dedicated foot clinics.

Future studies

Future observational studies need to include the characteristics of patients who were lost to follow-up, and should also attempt to explain the reasons for patients' withdrawal from studies. None of the sixteen studies included in the review measured adverse events from any of the diagnostic tests evaluated.

The predictive value of relatively simple clinical signs such as the presence or absence of leg and pedal pulses, skin colour, skin texture, hairlessness of the lower legs and condition of the toenails are not known. Clinical signs are potentially more cost-effective than more complex diagnostic tests, and are more feasible in community settings. Given that there are quite marked differences in cost between different tests, any new evidence about cost-effectiveness would deserve consideration. A diagnostic rule, based on elements of the clinical history, examination and available diagnostic tests needs to be developed, validated and tested to establish the effectiveness and cost-effectiveness of using such an approach when assessing the risk of diabetic foot ulceration in community settings.³²

Conclusions

Diagnostic tests and clinical signs are helpful in predicting the risk of diabetic foot ulceration. Evidence concerning the predictive value of simpler elements from the clinical history and examination is less clear. Future studies should assess the independent predictive value of all elements of patient history, physical signs and diagnostic tests when assessing the risk of diabetic foot ulceration.

Acknowledgements

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Standards of Medical Care in Diabetes—2014

American Diabetes Association

Diabetes mellitus is a complex, chronic illness requiring continuous medical care with multifactorial risk reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.

The American Diabetes Association's (ADA's) Standards of Care are intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care. The Standards of Care recommendations are not intended to preclude clinical judgment and must be applied in the context of excellent clinical care and with adjustments for individual preferences, comorbidities, and other patient factors. For more detailed information about management of diabetes, refer to references 1,2.

The recommendations include screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes. Many of these interventions have also been shown to be cost-effective (3). A grading system (**Table 1**) developed by ADA and modeled after existing methods was used to clarify and codify the evidence that forms the basis for the recommendations. The letters **A**, **B**, **C**, or **E** show the evidence level that supports each recommendation. The Standards of Care conclude with evidence and recommendations for strategies to improve the process of diabetes care. *It must be emphasized that clinical evidence and expert recommendations alone cannot improve patients' lives, but must be effectively translated into clinical management.*

I. CLASSIFICATION AND DIAGNOSIS

A. Classification

Diabetes can be classified into four clinical categories:

- Type 1 diabetes (due to β -cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance)
- Other specific types of diabetes due to other causes, e.g., genetic defects in β -cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes)

Some patients cannot be clearly classified as type 1 or type 2 diabetic. Clinical presentation and disease progression vary considerably in both types of diabetes. Occasionally, patients diagnosed with type 2 diabetes may present with ketoacidosis. Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia and occasionally with diabetic ketoacidosis (DKA). However, difficulties in diagnosis may occur in children, adolescents, and adults, with the true diagnosis becoming more obvious over time.

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Table 1—ADA evidence grading system for Clinical Practice Recommendations

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable RCTs that are adequately powered, including: <ul style="list-style-type: none"> • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., “all or none” rule developed by the Center for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted RCTs that are adequately powered, including: <ul style="list-style-type: none"> • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies <ul style="list-style-type: none"> • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies <ul style="list-style-type: none"> • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

B. Diagnosis of Diabetes

Diabetes is usually diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT) (4). Recently, an International Expert Committee added the A1C (threshold $\geq 6.5\%$) as a third option to diagnose diabetes (5) (Table 2).

A1C

The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care (POC) A1C assays may be NGSP-certified, proficiency testing is not mandated for performing the test, so use of these assays for diagnostic purposes may be problematic.

Epidemiological data show a similar relationship of A1C with the risk of retinopathy as seen with FPG and 2-h PG. The A1C has several advantages to the FPG and OGTT, including greater convenience (fasting not required), possibly greater preanalytical stability, and less day-to-day perturbations during stress and illness. These advantages must be balanced by greater

cost, the limited availability of A1C testing in certain regions of the developing world, and the incomplete correlation between A1C and average glucose in certain individuals.

Race/Ethnicity

A1C levels may vary with patients' race/ethnicity (6,7). Glycation rates may differ by race. For example, African Americans may have higher rates of glycation, but this is controversial. A recent epidemiological study found that, when matched for FPG, African Americans (with and without diabetes) had higher A1C than non-Hispanic whites, but also had higher levels of fructosamine and glycated albumin and lower levels of 1,5 anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (8). Epidemiological studies forming the framework for recommending A1C to diagnose diabetes have all been in adult populations. It is unclear if the same A1C cut point should be used to diagnose children or adolescents with diabetes (9,10).

Anemias/Hemoglobinopathies

Interpreting A1C levels in the presence of certain anemias and hemoglobinopathies is particularly problematic. For patients with an abnormal hemoglobin but normal red cell turnover, such as sickle cell trait, an A1C assay without interference from

abnormal hemoglobins should be used. An updated list is available at www.ngsp.org/interf.asp. In situations of abnormal red cell turnover, such as pregnancy, recent blood loss or transfusion, or some anemias, only blood glucose criteria should be used to diagnose diabetes.

Fasting and Two-Hour Plasma Glucose

In addition to the A1C test, the FPG and 2-h PG may also be used to diagnose diabetes. The current diagnostic criteria for diabetes are summarized in Table 2. The concordance between the FPG and 2-h PG tests is $<100\%$. The concordance between A1C and either glucose-based test is also imperfect. National Health and Nutrition Examination Survey (NHANES) data indicate that the A1C cut point of $\geq 6.5\%$ identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥ 126 mg/dL (7.0 mmol/L) (11). Numerous studies have confirmed that, at these cut points, the 2-h OGTT value diagnoses more screened people with diabetes (12). In reality, a large portion of the diabetic population remains undiagnosed. Of note, the lower sensitivity of A1C at the designated cut point may be offset by the test's ability to facilitate the diagnosis.

As with most diagnostic tests, a test result should be repeated *when feasible*

Table 2—Criteria for the diagnosis of diabetes

A1C $\geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

Two-hour PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

to rule out laboratory error (e.g., an elevated A1C should be repeated when feasible, and not necessarily in 3 months). Unless there is a clear clinical diagnosis (e.g., a patient in a hyperglycemic crisis or classic symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dL), it is preferable that the same test be repeated for confirmation, since there will be a greater likelihood of concurrence. For example, if the A1C is 7.0% and a repeat result is 6.8%, the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold, this also confirms the diagnosis.

On the other hand, if a patient has discordant results on two different tests, then the test result that is above the diagnostic cut point should be repeated. The diagnosis is made on the basis of the confirmed test. For example, if a patient meets the diabetes criterion of the A1C (two results $\geq 6.5\%$) but not the FPG (<126 mg/dL or 7.0 mmol/L), or vice versa, that person should be considered to have diabetes.

Since there is preanalytic and analytic variability of all the tests, it is possible that an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This is least likely for A1C, somewhat more likely for FPG, and most likely for the 2-h PG. Barring a laboratory error, such patients will likely have test results near the margins of the diagnostic threshold. The health care professional might opt to follow the patient closely and repeat the test in 3–6 months.

C. Categories of Increased Risk for Diabetes (Prediabetes)

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (13,14) recognized a group of individuals whose glucose levels did not meet the criteria for diabetes, but were too high to be considered normal. These persons were defined as having impaired fasting glucose (IFG) (FPG levels 100–125 mg/dL [5.6–6.9 mmol/L]), or impaired glucose tolerance (IGT) (2-h PG OGTT values of 140–199 mg/dL [7.8–11.0 mmol/L]). It should be noted that the World Health Organization (WHO) and a number of other diabetes organizations define the cutoff for IFG at 110 mg/dL (6.1 mmol/L).

“Prediabetes” is the term used for individuals with IFG and/or IGT, indicating the relatively high risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes and cardiovascular disease (CVD). IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with an A1C between 5.5 and 6.0% had a substantially increased risk of diabetes (5-year incidences from 9 to 25%). An A1C range of 6.0–6.5% had a 5-year risk of developing diabetes between 25–50%, and a relative risk (RR) 20 times higher compared with an A1C of 5.0% (15). In a community-based study of African American and non-Hispanic white adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (16). Other analyses suggest that an A1C of 5.7% is associated with similar diabetes risk to the high-risk participants in the Diabetes Prevention Program (DPP) (17).

Hence, it is reasonable to consider an A1C range of 5.7–6.4% as identifying individuals with prediabetes. As with those with IFG and IGT, individuals with an A1C of 5.7–6.4% should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section IV). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (15). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1Cs $>6.0\%$). **Table 3** summarizes the categories of prediabetes.

II. TESTING FOR DIABETES IN ASYMPTOMATIC PATIENTS

Recommendations

- Testing to detect type 2 diabetes and prediabetes in asymptomatic people should be considered in adults of any age who are overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$) and who have one or more additional risk factors for diabetes (**Table 4**). In those without these risk factors, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing at least at 3-year intervals is reasonable. **E**
- To test for diabetes or prediabetes, the A1C, FPG, or 2-h 75-g OGTT are appropriate. **B**
- In those identified with prediabetes, identify and, if appropriate, treat other CVD risk factors. **B**

The same tests are used for both screening and diagnosing diabetes. Diabetes may be identified anywhere along the spectrum of clinical scenarios: from a seemingly low-risk individual who happens to have glucose testing, to a higher-risk individual whom the provider tests because of high suspicion of diabetes, and finally, to the symptomatic patient. The discussion herein is primarily framed as testing for diabetes in asymptomatic individuals. The same assays used for testing will also detect individuals with prediabetes.

A. Testing for Type 2 Diabetes and Risk of Future Diabetes in Adults

Prediabetes and diabetes meet established criteria for conditions in which early detection is appropriate. Both conditions are common, are increasing in prevalence, and impose

Table 3—Categories of increased risk for diabetes (prediabetes)*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)

OR

2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

OR

A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

Table 4—Criteria for testing for diabetes in asymptomatic adult individuals

- Testing should be considered in all adults who are overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$) and have additional risk factors:
 - physical inactivity
 - first-degree relative with diabetes
 - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
 - women who delivered a baby weighing $>9 \text{ lb}$ or were diagnosed with GDM
 - hypertension ($\geq 140/90 \text{ mmHg}$ or on therapy for hypertension)
 - HDL cholesterol level $<35 \text{ mg/dL}$ (0.90 mmol/L) and/or a triglyceride level $>250 \text{ mg/dL}$ (2.82 mmol/L)
 - women with polycystic ovarian syndrome
 - A1C $\geq 5.7\%$, IGT, or IFG on previous testing
 - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
 - history of CVD
- In the absence of the above criteria, testing for diabetes should begin at age 45 years.
- If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

*At-risk BMI may be lower in some ethnic groups.

significant public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes is made. Simple tests to detect preclinical disease are readily available. The duration of glycemic burden is a strong predictor of adverse outcomes, and effective interventions exist to prevent progression of prediabetes to diabetes (see Section IV) and to reduce risk of complications of diabetes (see Section VI).

Type 2 diabetes is frequently not diagnosed until complications appear. Approximately one-fourth of the U.S. population may have undiagnosed diabetes. Mass screening of asymptomatic individuals has not effectively identified those with prediabetes or diabetes, and rigorous clinical trials to provide such proof are unlikely to occur. In a large randomized controlled trial (RCT) in Europe, general practice patients between the ages of 40–69 years were screened for diabetes, then randomized by practice to routine diabetes care or intensive treatment of multiple risk factors. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment. Incidence of first CVD event and mortality rates were not significantly different between groups (18). This study would seem to add support for early treatment of screen-detected diabetes, as risk factor control was excellent even in the routine treatment arm and both groups had lower event rates than predicted. The absence

of a control unscreened arm limits the ability to definitely prove that screening impacts outcomes. Mathematical modeling studies suggest that screening, independent of risk factors, beginning at age 30 or 45 years is highly cost-effective ($<\$11,000$ per quality-adjusted life-year gained) (19).

BMI Cut Points

Testing recommendations for diabetes in asymptomatic, undiagnosed adults are listed in **Table 4**. Testing should be considered in adults of any age with $\text{BMI} \geq 25 \text{ kg/m}^2$ and one or more of the known risk factors for diabetes. In addition to the listed risk factors, certain medications, such as glucocorticoids and antipsychotics (20), are known to increase the risk of type 2 diabetes. There is compelling evidence that lower BMI cut points suggest diabetes risk in some racial and ethnic groups. In a large multiethnic cohort study, for an equivalent incidence rate of diabetes conferred by a BMI of 30 kg/m^2 in non-Hispanic whites, the BMI cutoff value was 24 kg/m^2 in South Asians, 25 kg/m^2 in Chinese, and 26 kg/m^2 in African Americans (21). Disparities in screening rates, not explainable by insurance status, are highlighted by evidence that despite much higher prevalence of type 2 diabetes, ethnic minorities in an insured population are no more likely than non-Hispanic whites to be screened for diabetes (22). Because age is a major risk factor for diabetes, in those without these

risk factors, testing should begin at age 45 years.

The A1C, FPG, or the 2-h OGTT are appropriate for testing. It should be noted that the tests do not necessarily detect diabetes in the same individuals. The efficacy of interventions for primary prevention of type 2 diabetes (23–29) has primarily been demonstrated among individuals with IGT, not for individuals with isolated IFG or for individuals with specific A1C levels.

Testing Interval

The appropriate interval between tests is not known (30). The rationale for the 3-year interval is that false negatives will be repeated before substantial time elapses. It is also unlikely that an individual will develop significant complications of diabetes within 3 years of a negative test result. In the modeling study, repeat screening every 3 or 5 years was cost-effective (19).

Community Screening

Testing should be carried out within the health care setting because of the need for follow-up and discussion of abnormal results. Community screening outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. Conversely, there may be failure to ensure appropriate repeat testing for individuals who test negative. Community screening may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at low risk or even those already diagnosed.

B. Screening for Type 2 Diabetes in Children

Recommendation

- Testing to detect type 2 diabetes and prediabetes should be considered in children and adolescents who are overweight and who have two or more additional risk factors for diabetes (**Table 5**). **E**

In the last decade, the incidence of type 2 diabetes in adolescents has increased dramatically, especially in minority populations (31). As with adult recommendations, children and youth at increased risk for the presence or the development of type 2 diabetes should be tested within the health care setting (32).

A1C in Pediatrics

Recent studies question the validity of A1C in the pediatric population, especially in ethnic minorities, and suggest OGTT or FPG as more suitable diagnostic tests (33). However, many of these studies do not recognize that diabetes diagnostic criteria are based upon long-term health outcomes, and validations are not currently available in the pediatric population (34). ADA acknowledges the limited data supporting A1C for diagnosing diabetes in children and adolescents. However, aside from rare instances, such as cystic fibrosis and hemoglobinopathies, ADA continues to recommend A1C in this cohort (35,36). The modified recommendations of the ADA consensus statement "Type 2 Diabetes in Children and Adolescents" are summarized in **Table 5**.

C. Screening for Type 1 Diabetes

Recommendation

- Inform type 1 diabetic patients of the opportunity to have their relatives screened for type 1 diabetes risk in the setting of a clinical research study. **E**

Type 1 diabetic patients often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and some cases are diagnosed with life-threatening ketoacidosis. The incidence

and prevalence of type 1 diabetes is increasing (31,37,38). Several studies suggest that measuring islet autoantibodies in relatives of those with type 1 diabetes may identify individuals who are at risk for developing type 1 diabetes. Such testing, coupled with education about diabetes symptoms and close follow-up in an observational clinical study, may enable earlier identification of type 1 diabetes onset. A recent study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (39,40). These findings are highly significant because, while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and Colorado groups were recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and genetic cases of type 1 diabetes. There is evidence to suggest that early diagnosis may limit acute complications (39) and extend long-term endogenous insulin production (41). While there is currently a lack of accepted screening programs, one should consider referring relatives of those with type 1 diabetes for antibody testing for risk assessment in the setting of a clinical research study (<http://www2.diabetestrialnet.org>).

Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended. Higher-risk individuals may be screened, but only in the context of a clinical research setting. Individuals who screen positive will be counseled about the risk of developing diabetes, diabetes symptoms, and the prevention of DKA. Numerous clinical studies are being conducted to test various methods of preventing type 1 diabetes in those with evidence of autoimmunity (www.clinicaltrials.gov).

III. DETECTION AND DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS

Recommendations

- Screen for undiagnosed type 2 diabetes at the first prenatal visit in

those with risk factors, using standard diagnostic criteria. **B**

- Screen for GDM at 24–28 weeks of gestation in pregnant women not previously known to have diabetes. **A**
- Screen women with GDM for persistent diabetes at 6–12 weeks postpartum, using the OGTT and nonpregnancy diagnostic criteria. **E**
- Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**
- Women with a history of GDM found to have prediabetes should receive lifestyle interventions or metformin to prevent diabetes. **A**
- Further research is needed to establish a uniform approach to diagnosing GDM. **E**

For many years, GDM was defined as any degree of glucose intolerance with onset or first recognition during pregnancy (13), whether or not the condition persisted after pregnancy, and not excluding the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but its limitations were recognized for many years. As the ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, the number of pregnant women with undiagnosed type 2 diabetes has increased (42). Because of this, it is reasonable to screen women with risk factors for type 2 diabetes (**Table 4**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2**). Women with diabetes in the first trimester should receive a diagnosis of overt, not gestational, diabetes.

GDM carries risks for the mother and neonate. Not all adverse outcomes are of equal clinical importance. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (43), a large-scale (~25,000 pregnant women) multinational epidemiological study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28

Table 5—Testing for type 2 diabetes in asymptomatic children*

Criteria

- Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

Plus any two of the following risk factors:

- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, or small-for-gestational-age birth weight)
- Maternal history of diabetes or GDM during the child's gestation

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: every 3 years

*Persons aged 18 years and younger.

weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM. GDM screening can be accomplished with either of two strategies:

1. "One-step" 2-h 75-g OGTT or
2. "Two-step" approach with a 1-h 50-g (nonfasting) screen followed by a 3-h 100-g OGTT for those who screen positive (Table 6)

Different diagnostic criteria will identify different magnitudes of maternal hyperglycemia and maternal/fetal risk.

In the 2011 Standards of Care (44), ADA for the first time recommended that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation based on an International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus meeting (45). Diagnostic cut points for the fasting, 1-h, and 2-h PG measurements were defined that conveyed an odds ratio for adverse outcomes of at least 1.75 compared with women with the mean glucose levels in the HAPO study, a strategy anticipated to significantly increase the prevalence of GDM (from 5–6% to ~15–20%), primarily because only one abnormal value, not two, is sufficient to make the diagnosis. ADA recognized that the anticipated increase in the incidence of GDM diagnosed by these criteria would have significant impact on the costs, medical infrastructure capacity, and potential for increased "medicalization" of pregnancies previously categorized as normal, but recommended these diagnostic criteria changes in the context of worrisome worldwide increases in obesity and diabetes rates with the intent of optimizing gestational outcomes for women and their babies. It is important to note that 80–90% of women in both of the mild GDM studies (whose glucose values overlapped with the thresholds recommended herein) could be managed with lifestyle therapy alone. The expected benefits to these pregnancies and offspring are inferred from intervention trials that focused on women with lower levels of

Table 6—Screening for and diagnosis of GDM

"One-step" (IADPSG consensus)

Perform a 75-g OGTT, with plasma glucose measurement fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of GDM is made when any of the following plasma glucose values are exceeded:

- Fasting: ≥ 92 mg/dL (5.1 mmol/L)
- 1 h: ≥ 180 mg/dL (10.0 mmol/L)
- 2 h: ≥ 153 mg/dL (8.5 mmol/L)

"Two-step" (NIH consensus)

Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h (Step 1), at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. If the plasma glucose level measured 1 h after the load is ≥ 140 mg/dL* (7.8 mmol/L), proceed to 100-g OGTT (Step 2). The 100-g OGTT should be performed when the patient is fasting. The diagnosis of GDM is made when at least two of the following four plasma glucose levels (measured fasting, 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan	or	NDDG
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group. *The American College of Obstetricians and Gynecologists (ACOG) recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic minorities with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

hyperglycemia than identified using older GDM diagnostic criteria and that found modest benefits including reduced rates of large-for-gestational-age (LGA) births (46,47). However, while treatment of lower threshold hyperglycemia can reduce LGA, it has not been shown to reduce primary cesarean delivery rates. Data are lacking on how treatment of lower threshold hyperglycemia impacts prognosis of future diabetes for the mother and future obesity, diabetes risk, or other metabolic consequences for the offspring. The frequency of follow-up and blood glucose monitoring for these women has also not yet been standardized, but is likely to be less intensive than for women diagnosed by the older criteria.

National Institutes of Health Consensus Report

Since this initial IADPSG recommendation, the National Institutes of Health (NIH) completed a consensus development conference involving a 15-member panel with representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields (48). Reviewing the same available data, the NIH consensus panel recommended continuation of the "two-step"

approach of screening with a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screen positive, a strategy commonly used in the U.S. Key factors reported in the NIH panel's decision-making process were the lack of clinical trial interventions demonstrating the benefits of the "one-step" strategy and the potential negative consequences of identifying a large new group of women with GDM. Moreover, screening with a 50-g GLT does not require fasting and is therefore easier to accomplish for many women. Treatment of higher threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, LGA, and shoulder dystocia, without increasing small-for-gestational-age births (49).

How do two different groups of experts arrive at different GDM screening and diagnosis recommendations? Because glycemic dysregulation exists on a continuum, the decision to pick a single binary threshold for diagnosis requires balancing the harms and benefits associated with greater versus lesser sensitivity. While data from the HAPO study demonstrated a correlation between increased fasting glucose levels identified through the "one-step" strategy with increased odds for adverse

pregnancy outcomes, this large observational study was not designed to determine the benefit of intervention. Moreover, there are no available cost-effective analyses to examine the balance of achieved benefits versus the increased costs generated by this strategy.

The conflicting recommendations from these two consensus panels underscore several key points:

1. There are insufficient data to strongly demonstrate the superiority of one strategy over the other.
2. The decision of which strategy to implement must therefore be made based on the relative values placed on currently unmeasured factors (e.g., cost-benefit estimation, willingness to change practice based on correlation studies rather than clinical intervention trial results, relative role of cost considerations, and available infrastructure).
3. Further research is needed to resolve these uncertainties.

There remains strong consensus that establishing a uniform approach to diagnosing GDM will have extensive benefits for patients, caregivers, and policymakers. Longer-term outcome studies are currently underway.

Because some cases of GDM may represent preexisting undiagnosed type 2 diabetes, women with a history of GDM should be screened for diabetes 6–12 weeks postpartum, using nonpregnant OGTT criteria. Because of their antepartum treatment for hyperglycemia, A1C for diagnosis of persistent diabetes at the postpartum visit is not recommended (50). Women with a history of GDM have a greatly increased subsequent diabetes risk (51) and should be followed up with subsequent screening for the development of diabetes or prediabetes, as outlined in Section II. Lifestyle interventions or metformin should be offered to women with a history of GDM who develop prediabetes, as discussed in Section IV. In the prospective Nurses' Health Study II, subsequent diabetes risk after a history of GDM was significantly lower in women who followed healthy eating

patterns. Adjusting for BMI moderately, but not completely, attenuated this association (52).

IV. PREVENTION/DELAY OF TYPE 2 DIABETES

Recommendations

- Patients with IGT **A**, IFG **E**, or an A1C 5.7–6.4% **E** should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week of moderate activity such as walking.
- Follow-up counseling appears to be important for success. **B**
- Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. **B**
- Metformin therapy for prevention of type 2 diabetes may be considered in those with IGT **A**, IFG **E**, or an A1C 5.7–6.4% **E**, especially for those with BMI >35 kg/m², aged <60 years, and women with prior GDM. **A**
- At least annual monitoring for the development of diabetes in those with prediabetes is suggested. **E**
- Screening for and treatment of modifiable risk factors for CVD is suggested. **B**

RCTs have shown that individuals at high risk for developing type 2 diabetes (IFG, IGT, or both) can significantly decrease the rate of diabetes onset with particular interventions (23–29). These include intensive lifestyle modification programs that have been shown to be very effective (~58% reduction after 3 years) and pharmacological agents metformin, α -glucosidase inhibitors, orlistat, and thiazolidinediones, each of which has been shown to decrease incident diabetes to various degrees. Follow-up of all three large studies of lifestyle intervention has shown sustained reduction in the rate of conversion to type 2 diabetes, with 43% reduction at 20 years in the Da Qing study (53), 43% reduction at 7 years in the Finnish Diabetes Prevention Study (DPS) (54), and 34% reduction at 10 years in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS) (55). A cost-effectiveness model suggested that lifestyle interventions as delivered

in the DPP are cost-effective (56), and actual cost data from the DPP and DPPOS confirm that lifestyle interventions are highly cost-effective (57). Group delivery of the DPP intervention in community settings has the potential to be significantly less expensive while still achieving similar weight loss (58). The Centers for Disease Control and Prevention (CDC) helps coordinate the National Diabetes Prevention Program, a resource designed to bring evidence-based lifestyle change programs for preventing type 2 diabetes to communities (<http://www.cdc.gov/diabetes/prevention/index.htm>).

Given the clinical trial results and the known risks of progression of prediabetes to diabetes, persons with an A1C of 5.7–6.4%, IGT, or IFG should be counseled on lifestyle changes with goals similar to those of the DPP (7% weight loss and moderate physical activity of at least 150 min/week). Metformin has a strong evidence base and demonstrated long-term safety as pharmacological therapy for diabetes prevention (59). For other drugs, cost, side effects, and lack of a persistent effect require consideration (60).

Metformin

Metformin was less effective than lifestyle modification in the DPP and DPPOS, but may be cost-saving over a 10-year period (57). It was as effective as lifestyle modification in participants with a BMI ≥ 35 kg/m², but not significantly better than placebo in those over age 60 years (23). In the DPP, for women with a history of GDM, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (61). Metformin therefore might reasonably be recommended for very-high-risk individuals (e.g., history of GDM, very obese, and/or those with more severe or progressive hyperglycemia).

People with prediabetes often have other cardiovascular risk factors, such as obesity, hypertension, and dyslipidemia, and are at increased risk for CVD events. While treatment goals are the same as for other patients without diabetes, increased vigilance is warranted to identify and treat these and other risk factors (e.g., smoking).

V. DIABETES CARE

A. Initial Evaluation

A complete medical evaluation should be performed to classify the diabetes, detect the presence of diabetes complications, review previous treatment and risk factor control in patients with established diabetes, assist in formulating a management plan, and provide a basis for continuing care. Laboratory tests appropriate to the evaluation of each patient's medical condition should be completed. A focus on the components of comprehensive care (Table 7) will

enable the health care team to optimally manage the patient with diabetes.

B. Management

People with diabetes should receive medical care from a team that may include physicians, nurse practitioners, physician's assistants, nurses, dietitians, pharmacists, and mental health professionals with expertise in diabetes. In this collaborative and integrated team approach, the individuals with diabetes must also assume an active role in their care.

The management plan should be formulated as a collaborative therapeutic alliance among the patient and family, the physician, and other members of the health care team. A variety of strategies and techniques should be used to provide adequate education and development of problem-solving skills in the numerous aspects of diabetes management. Treatment goals and plans should be individualized and take patient preferences into account. The management plan should recognize diabetes self-management education (DSME) and ongoing diabetes support as integral components of care. In developing the plan, consideration should be given to the patient's age, school or work schedule and conditions, physical activity, eating patterns, social situation and cultural factors, presence of diabetes complications, health priorities, and other medical conditions.

C. Glycemic Control

1. Assessment of Glycemic Control

Two primary techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control: patient self-monitoring of blood glucose (SMBG) or interstitial glucose, and A1C.

a. Glucose Monitoring

Recommendations

- Patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. **B**
- When prescribed as part of a broader educational context, SMBG results may be helpful to guide treatment decisions and/or patient self-management for patients using less frequent insulin injections or noninsulin therapies. **E**
- When prescribing SMBG, ensure that patients receive ongoing instruction and regular evaluation of SMBG technique and SMBG results, as well as their ability to use SMBG data to adjust therapy. **E**
- When used properly, continuous glucose monitoring (CGM) in

Table 7—Components of the comprehensive diabetes evaluation

Medical history

- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)
- Current treatment of diabetes, including medications, medication adherence and barriers thereto, meal plan, physical activity patterns, and readiness for behavior change
- Results of glucose monitoring and patient's use of data
- DKA frequency, severity, and cause
- Hypoglycemic episodes
 - Hypoglycemia awareness
 - Any severe hypoglycemia: frequency and cause
- History of diabetes-related complications
 - Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
 - Macrovascular: CHD, cerebrovascular disease, and PAD
 - Other: psychosocial problems,* dental disease*

Physical examination

- Height, weight, BMI
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination*
- Thyroid palpation
- Skin examination (for acanthosis nigricans and insulin injection sites)
- Comprehensive foot examination
 - Inspection
 - Palpation of dorsalis pedis and posterior tibial pulses
 - Presence/absence of patellar and Achilles reflexes
 - Determination of proprioception, vibration, and monofilament sensation

Laboratory evaluation

- A1C, if results not available within past 2–3 months
- If not performed/available within past year
 - Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides
 - Liver function tests
 - Test for urine albumin excretion with spot urine albumin-to-creatinine ratio
 - Serum creatinine and calculated GFR
 - TSH in type 1 diabetes, dyslipidemia, or women over age 50 years

Referrals

- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for MNT
- DSME
- Dentist for comprehensive periodontal examination
- Mental health professional, if needed

*See appropriate referrals for these categories.

conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged ≥ 25 years) with type 1 diabetes. **A**

- Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. **C**
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. **E**

Major clinical trials of insulin-treated patients that demonstrated the benefits of intensive glycemic control on diabetes complications have included SMBG as part of multifactorial interventions, suggesting that SMBG is a component of effective therapy. SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. Results of SMBG can be useful in preventing hypoglycemia and adjusting medications (particularly prandial insulin doses), medical nutrition therapy (MNT), and physical activity. Evidence also supports a correlation between SMBG frequency and lower A1C (62).

SMBG frequency and timing should be dictated by the patient's specific needs and goals. SMBG is especially important for patients treated with insulin to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia. Most patients with type 1 diabetes or on intensive insulin regimens (MDI or insulin pump therapy) should consider SMBG prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. For many patients, this will require testing 6–8 times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjustment for multiple confounders, increased daily frequency of SMBG was significantly associated with lower A1C (-0.2% per additional test per day, leveling off at five tests per day) and with fewer acute

complications (63). For patients on nonintensive insulin regimens, such as those with type 2 diabetes on basal insulin, when to prescribe SMBG and the testing frequency are unclear because there is insufficient evidence for testing in this cohort.

Several randomized trials have called into question the clinical utility and cost-effectiveness of routine SMBG in noninsulin-treated patients (64–66). A recent meta-analysis suggested that SMBG reduced A1C by 0.25% at 6 months (67), but a Cochrane review concluded that the overall effect of SMBG in such patients is minimal up to 6 months after initiation and subsides after 12 months (68). A key consideration is that SMBG alone does not lower blood glucose level; to be useful, the information must be integrated into clinical and self-management plans.

SMBG accuracy is instrument and user dependent (69), so it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Optimal use of SMBG requires proper review and interpretation of the data, both by the patient and provider. Among patients who checked their blood glucose at least once daily, many reported taking no action when results were high or low (70). In one study of insulin-naïve patients with suboptimal initial glycemic control, use of structured SMBG (a paper tool to collect and interpret 7-point SMBG profiles over 3 days at least quarterly) reduced A1C by 0.3% more than an active control group (71). Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacological therapy to achieve specific goals. The ongoing need for and frequency of SMBG should be reevaluated at each routine visit.

Continuous Glucose Monitoring

Real-time CGM through the measurement of interstitial glucose (which correlates well with plasma glucose) is available. These sensors require calibration with SMBG, and the latter are still required for making acute treatment decisions. CGM devices have alarms for hypo- and hyperglycemic excursions. A 26-week randomized trial

of 322 type 1 diabetic patients showed that adults aged ≥ 25 years using intensive insulin therapy and CGM experienced a 0.5% reduction in A1C (from ~ 7.6 to 7.1%) compared with usual intensive insulin therapy with SMBG (72). Sensor use in those < 25 years of age (children, teens, and adults) did not result in significant A1C lowering, and there was no significant difference in hypoglycemia in any group. The greatest predictor of A1C lowering for all age-groups was frequency of sensor use, which was lower in younger age-groups. In a smaller RCT of 129 adults and children with baseline A1C $< 7.0\%$, outcomes combining A1C and hypoglycemia favored the group using CGM, suggesting that CGM is also beneficial for individuals with type 1 diabetes who have already achieved excellent control (72).

Overall, meta-analyses suggest that compared with SMBG, CGM use is associated with A1C lowering by $\sim 0.26\%$ (73). The technology may be particularly useful in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes, although studies have not shown significant reductions in severe hypoglycemia (73). A CGM device equipped with an automatic low glucose suspend feature was recently approved by the U.S. Food and Drug Administration (FDA). The ASPIRE trial of 247 patients showed that sensor-augmented insulin pump therapy with a low glucose suspend significantly reduced nocturnal hypoglycemia, without increasing A1C levels for those over 16 years of age (74). These devices may offer the opportunity to reduce severe hypoglycemia for those with a history of nocturnal hypoglycemia. CGM forms the underpinning for the "artificial pancreas" or the closed-loop system. However, before CGM is widely adopted, data must be reported and analyzed using a standard universal template that is predictable and intuitive (75).

b. A1C

Recommendations

- Perform the A1C test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**
- Perform the A1C test quarterly in patients whose therapy has changed

or who are not meeting glycemic goals. **E**

- Use of POC testing for A1C provides the opportunity for more timely treatment changes. **E**

A1C reflects average glycemia over several months (69) and has strong predictive value for diabetes complications (76,77). Thus, A1C testing should be performed routinely in all patients with diabetes: at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether a patient's glycemic targets have been reached and maintained. The frequency of A1C testing should be dependent on the clinical situation, the treatment regimen used, and the clinician's judgment. Some patients with stable glycemia well within target may do well with testing only twice per year. Unstable or highly intensively managed patients (e.g., pregnant type 1 diabetic women) may require testing more frequently than every 3 months.

A1C Limitations

As mentioned above, the A1C test is subject to certain limitations. Conditions that affect erythrocyte turnover (hemolysis, blood loss) and hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's clinical situation (69). A1C also does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially type 1 diabetic patients or type 2 diabetic patients with severe insulin deficiency, glycemic control is best evaluated by the combination of results from self-monitoring and the A1C. The A1C may also confirm the accuracy of the patient's meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

A1C and Plasma Glucose

Table 8 contains the correlation between A1C levels and mean plasma glucose levels based on data from the international A1C-Derived Average Glucose (ADAG) trial using frequent SMBG and CGM in 507 adults (83% non-Hispanic whites) with type 1, type 2, and no diabetes (78). The ADA and the American Association for Clinical

Table 8—Correlation of A1C with average glucose

A1C (%)	Mean plasma glucose	
	mg/dL	mmol/L
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92 (ref. 78). A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at <http://professional.diabetes.org/eAG>.

Chemistry have determined that the correlation ($r = 0.92$) is strong enough to justify reporting both the A1C result and an estimated average glucose (eAG) result when a clinician orders the A1C test. The table in pre-2009 versions of the Standards of Medical Care in Diabetes describing the correlation between A1C and mean glucose was derived from relatively sparse data (one 7-point profile over 1 day per A1C reading) in the primarily non-Hispanic white type 1 diabetic participants in the DCCT (79). Clinicians should note that the numbers in the table are now different because they are based on ~2,800 readings per A1C in the ADAG trial.

In the ADAG study, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although there was a trend toward a difference between the African/African American and non-Hispanic white cohorts. A small study comparing A1C to CGM data in type 1 diabetic children found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation ($r = 0.7$) was significantly lower than in the ADAG trial (80). Whether there are significant differences in how A1C relates to average glucose in children or in African American patients is an area for further study (33,81). For the time being, the question has not led to different recommendations about testing A1C or

to different interpretations of the clinical meaning of given levels of A1C in those populations.

For patients in whom A1C/eAG and measured blood glucose appear discrepant, clinicians should consider the possibilities of hemoglobinopathy or altered red cell turnover, and the options of more frequent and/or different timing of SMBG or use of CGM. Other measures of chronic glycemia such as fructosamine are available, but their linkage to average glucose and their prognostic significance are not as clear as for A1C.

2. Glycemic Goals in Adults

Recommendations

- Lowering A1C to below or around 7% has been shown to reduce microvascular complications of diabetes and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease. Therefore, a reasonable A1C goal for many nonpregnant adults is <7%. **B**
- Providers might reasonably suggest more stringent A1C goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD. **C**
- Less stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and in those with long-standing diabetes in whom the general goal is difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. **B**

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The DCCT study (76), a prospective RCT of intensive versus standard glycemic control in patients with relatively recently diagnosed type 1 diabetes showed definitively that improved glycemic

control is associated with significantly decreased rates of microvascular (retinopathy and nephropathy) and neuropathic complications. Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (82,83) demonstrated persistence of these microvascular benefits in previously intensively treated subjects, even though their glycemic control approximated that of previous standard arm subjects during follow-up.

Kumamoto and UK Prospective Diabetes Study

The Kumamoto (84) and UK Prospective Diabetes Study (UKPDS) (85,86) confirmed that intensive glycemic control was associated with significantly decreased rates of microvascular and neuropathic complications in type 2 diabetic patients. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (87). Three landmark trials (ACCORD, ADVANCE, and VADT, described in further detail below) were designed to examine the impact of intensive A1C control on CVD outcomes and showed that lower A1C levels were associated with reduced onset or progression of microvascular complications (88–90).

Epidemiological analyses of the DCCT and UKPDS (76,77) demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair/good control. These analyses also suggest that further lowering of A1C from 7 to 6% is associated with further reduction in the risk of microvascular complications, though the absolute risk reductions become much smaller. Given the substantially increased risk of hypoglycemia in type 1 diabetes trials, and now seen in recent type 2 diabetes trials, the risks of lower glycemic targets may outweigh the potential benefits on microvascular complications on a population level. The concerning mortality findings in the ACCORD trial (91) and the relatively much greater effort required to achieve near-euglycemia should also be considered

when setting glycemic targets.

However, based on physician judgment and patient preferences, select patients, especially those with little comorbidity and long life expectancy, may benefit from adopting more intensive glycemic targets (e.g., A1C target <6.5%) as long as significant hypoglycemia does not become a barrier.

Cardiovascular Disease Outcomes

CVD is a more common cause of death than microvascular complications in populations with diabetes. However, it is less clearly impacted by hyperglycemia levels or intensity of glycemic control. In the DCCT, there was a trend toward lower risk of CVD events with intensive control. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction (MI), stroke, or CVD death compared with those previously in the standard arm (92). The benefit of intensive glycemic control in this type 1 diabetic cohort has recently been shown to persist for several decades (93).

In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. During the UKPDS trial, there was a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance ($P = 0.052$), and there was no suggestion of benefit on other CVD outcomes (e.g., stroke). However, after 10 years of follow-up, those originally randomized to intensive glycemic control had significant long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy) and in all-cause mortality (13% and 27%, respectively) (87).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT) studies suggested no significant reduction in CVD outcomes with intensive glycemic control in participants who had more advanced type 2 diabetes than UKPDS participants. All three trials were conducted in participants with more long-standing diabetes (mean duration 8–11 years) and

either known CVD or multiple cardiovascular risk factors. Details of these studies are reviewed extensively in an ADA position statement (94).

ACCORD

The ACCORD study participants had either known CVD or two or more major cardiovascular risk factors and were randomized to intensive glycemic control (goal A1C <6%) or standard glycemic control (goal A1C 7–8%). The glycemic control comparison was halted early due to an increased mortality rate in the intensive compared with the standard arm (1.41 vs. 1.14%/year; hazard ratio [HR] 1.22 [95% CI 1.01–1.46]); with a similar increase in cardiovascular deaths. Initial analysis of the ACCORD data (evaluating variables including weight gain, use of any specific drug or drug combination, and hypoglycemia) did not identify a clear explanation for the excess mortality in the intensive arm (91). A subsequent analysis showed no increase in mortality in the intensive arm participants who achieved A1C levels below 7%, nor in those who lowered their A1C quickly after trial enrollment. There was no A1C level at which intensive versus standard arm participants had significantly lower mortality. The highest risk for mortality was observed in intensive arm participants with the highest A1C levels (95). Severe hypoglycemia was significantly more likely in participants randomized to the intensive glycemic control arm. Unlike the DCCT, where lower achieved A1C levels were related to significantly increased rates of severe hypoglycemia, in ACCORD every 1% decline in A1C from baseline to 4 months into the trial was associated with a significant decrease in the rate of severe hypoglycemia in both arms (95).

ADVANCE

The primary outcome of ADVANCE was a combination of microvascular events (nephropathy and retinopathy) and major adverse cardiovascular events (MI, stroke, and cardiovascular death). Intensive glycemic control (A1C <6.5%, vs. treatment to local standards) significantly reduced the primary end point, primarily due to a significant reduction in the microvascular outcome, specifically development of albuminuria (>300 mg/24 h), with

no significant reduction in the macrovascular outcome. There was no difference in overall or cardiovascular mortality between the two arms (89).

VADT

The primary outcome of the VADT was a composite of CVD events. The trial randomized type 2 diabetic participants who were uncontrolled on insulin or on maximal dose oral agents (median entry A1C 9.4%) to a strategy of intensive glycemic control (goal A1C <6.0%) or standard glycemic control, with a planned A1C separation of at least 1.5%. The cumulative primary outcome was nonsignificantly lower in the intensive arm (88). An ancillary study of the VADT demonstrated that intensive glycemic control significantly reduced the primary CVD outcome in individuals with less atherosclerosis at baseline but not in persons with more extensive baseline atherosclerosis (96). A post hoc analysis showed that mortality in the intensive versus standard glycemic control arm was related to duration of diabetes at study enrollment. Those with diabetes duration less than 15 years had a mortality benefit in the intensive arm, while those with duration of 20 years or more had higher mortality in the intensive arm (97).

The evidence for a cardiovascular benefit of intensive glycemic control primarily rests on long-term follow-up of study cohorts treated early in the course of type 1 and type 2 diabetes, and a subset analyses of ACCORD, ADVANCE, and VADT. A group-level meta-analysis of the latter three trials suggests that glucose lowering has a modest (9%) but statistically significant reduction in major CVD outcomes, primarily nonfatal MI, with no significant effect on mortality. However, heterogeneity of the mortality effects across studies was noted. A prespecified subgroup analysis suggested that major CVD outcome reduction occurred in patients without known CVD at baseline (HR 0.84 [95% CI 0.74–0.94]) (98). Conversely, the mortality findings in ACCORD and subgroup analyses of the VADT suggest that the potential risks of intensive glycemic control may outweigh its benefits in some patients. Those with long duration of diabetes, known history of severe hypoglycemia,

advanced atherosclerosis, and advanced age/frailty may benefit from less aggressive targets. Providers should be vigilant in preventing severe hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal A1C levels in patients in whom such targets cannot be safely and reasonably achieved. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals. Many factors, including patient preferences, should be taken into account when developing a patient's individualized goals (99) (**Fig. 1**).

Glycemic Goals

Recommended glycemic goals for many nonpregnant adults are shown in **Table 9**. The recommendations are based on those for A1C values, with blood glucose levels that appear to correlate with achievement of an A1C of <7%. The issue of pre- versus postprandial SMBG targets is complex (100). Elevated postchallenge (2-h OGTT) glucose values have been

associated with increased cardiovascular risk independent of FPG in some epidemiological studies. In diabetic subjects, surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia (101). It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being greater at A1C levels that are closer to 7%. However, outcome studies have clearly shown A1C to be the primary predictor of complications, and landmark glycemic control trials such as the DCCT and UKPDS relied overwhelmingly on preprandial SMBG. Additionally, an RCT in patients with known CVD found no CVD benefit of insulin regimens targeting postprandial glucose compared with those targeting preprandial glucose (102). A reasonable recommendation for postprandial testing and targets is that for individuals who have premeal glucose values within target but have A1C values above target, monitoring postprandial plasma glucose (PPG) 1–2 h after the start of the meal and treatment aimed at reducing

Approach to management of hyperglycemia:

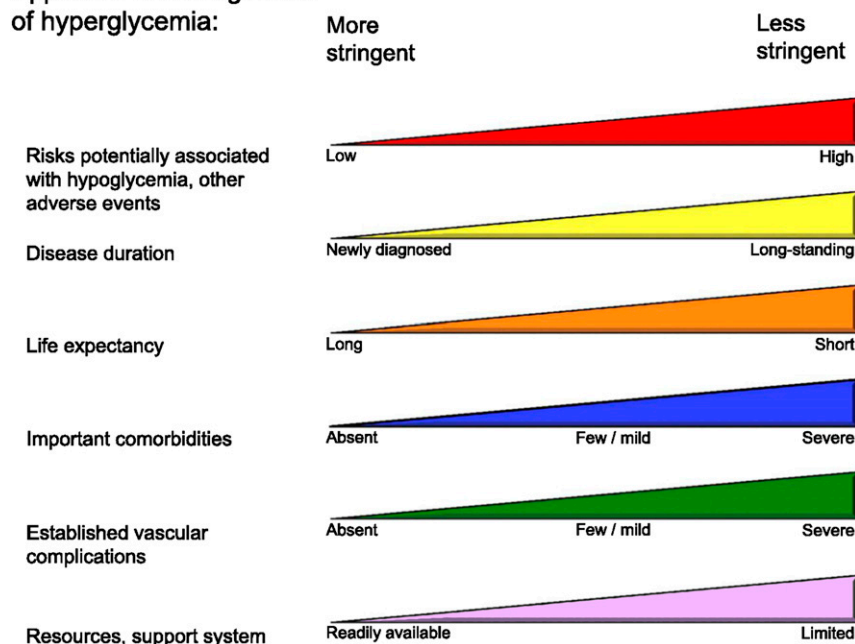


Figure 1—Approach to management of hyperglycemia. Depiction of the elements of decision making used to determine appropriate efforts to achieve glycemic targets. Characteristics/predicaments toward the left justify more stringent efforts to lower A1C, whereas those toward the right are compatible with less stringent efforts. Where possible, such decisions should be made in conjunction with the patient, reflecting his or her preferences, needs, and values. This “scale” is not designed to be applied rigidly but to be used as a broad construct to help guide clinical decisions. Adapted with permission from Ismail-Beigi et al. (99).

Table 9—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0%*
Preprandial capillary plasma glucose	70–130 mg/dL* (3.9–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)
• *Goals should be individualized based on: <ul style="list-style-type: none"> • duration of diabetes • age/life expectancy • comorbid conditions • known CVD or advanced microvascular complications • hypoglycemia unawareness • individual patient considerations 	
• More or less stringent glycemic goals may be appropriate for individual patients	
• Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals	

†Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

PPG values to <180 mg/dL may help lower A1C.

Glycemic goals for children are provided in Section VIII.A.1.a.

Glycemic Goals in Pregnant Women

The goals for glycemic control for women with GDM are based on recommendations from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (103) and have the following targets for maternal capillary glucose concentrations:

- Preprandial: ≤ 95 mg/dL (5.3 mmol/L), and either:
- 1-h postmeal: ≤ 140 mg/dL (7.8 mmol/L) or
- 2-h postmeal: ≤ 120 mg/dL (6.7 mmol/L)

For women with preexisting type 1 or type 2 diabetes who become pregnant, the following are recommended as optimal glycemic goals, if they can be achieved without excessive hypoglycemia (104):

- Premeal, bedtime, and overnight glucose 60–99 mg/dL (3.3–5.4 mmol/L)
- Peak postprandial glucose 100–129 mg/dL (5.4–7.1 mmol/L)
- A1C <6.0%

D. Pharmacological and Overall Approaches to Treatment

1. Insulin Therapy for Type 1 Diabetes

- Most people with type 1 diabetes should be treated with MDI injections

(three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII). **A**

- Most people with type 1 diabetes should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. **E**
- Most people with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk. **A**

Screening

- Consider screening those with type 1 diabetes for other autoimmune diseases (thyroid, vitamin B₁₂ deficiency, celiac) as appropriate. **B**

The DCCT clearly showed that intensive insulin therapy (three or more injections per day of insulin, or CSII [or insulin pump therapy]) was a key part of improved glycemia and better outcomes (76,92). The study was carried out with short- and intermediate-acting human insulins. Despite better microvascular outcomes, intensive insulin therapy was associated with a high rate of severe hypoglycemia (62 episodes per 100 patient-years of therapy). Since the DCCT, a number of rapid-acting and long-acting insulin analogs have been developed. These analogs are associated with less hypoglycemia with equal A1C lowering in type 1 diabetes (105,106).

Recommended therapy for type 1 diabetes consists of the following components:

1. Use MDI injections (3–4 injections per day of basal and prandial insulin) or CSII therapy.
2. Match prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated activity.
3. For most patients (especially with hypoglycemia), use insulin analogs.
4. For patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness, use of sensor-augmented low glucose suspend threshold pump may be considered.

There are excellent reviews to guide the initiation and management of insulin therapy to achieve desired glycemic goals (105,107,108). Although most studies of MDI versus pump therapy have been small and of short duration, a systematic review and meta-analysis concluded that there were no systematic differences in A1C or severe hypoglycemia rates in children and adults between the two forms of intensive insulin therapy (73). Recently, a large randomized trial in type 1 diabetic patients with nocturnal hypoglycemia reported that sensor-augmented insulin pump therapy with the threshold-suspend feature reduced nocturnal hypoglycemia, without increasing glycated hemoglobin values (74). Overall, intensive management through pump therapy/CGM and active patient/family participation should be strongly encouraged (109–111). For selected individuals who have mastered carbohydrate counting, education on the impact of protein and fat on glycemic excursions can be incorporated into diabetes management (112).

Screening

Because of the increased frequency of other autoimmune diseases in type 1 diabetes, screening for thyroid dysfunction, vitamin B₁₂ deficiency, and celiac disease should be considered based on signs and symptoms. Periodic screening in asymptomatic individuals has been recommended, but the effectiveness and optimal frequency are unclear.

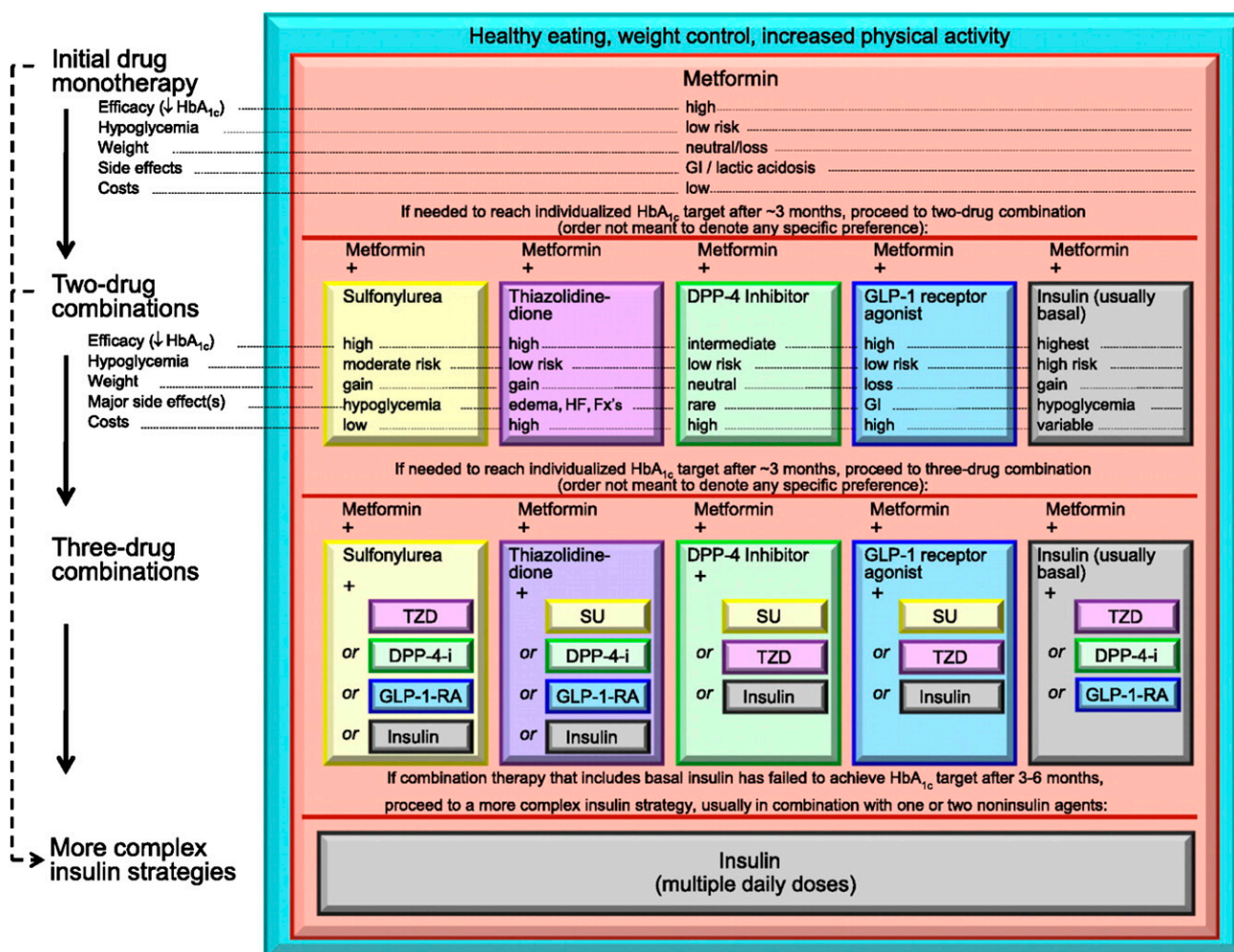


Figure 2—Antihyperglycemic therapy in type 2 diabetes: general recommendations. DPP-4-i, DPP-4 inhibitor; Fx's, bone fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; HF, heart failure; SU, sulfonylurea; TZD, thiazolidinedione. For further details, see ref. 113. Adapted with permission.

2. Pharmacological Therapy for Hyperglycemia in Type 2 Diabetes

Recommendations

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. **A**
- In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset. **E**
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin. **A**
- A patient-centered approach should be used to guide choice of pharmacological agents.

Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. **E**

- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. **B**

The ADA and the European Association for the Study of Diabetes (EASD) formed a joint task force to evaluate the data and develop recommendations for the use of antihyperglycemic agents in type 2 diabetic patients (113). This 2012 position statement is less prescriptive than prior algorithms and discusses advantages and disadvantages of the available medication classes and considerations for their use. A patient-centered approach is stressed, including patient preferences, cost and potential side effects of each class, effects

on body weight, and hypoglycemia risk. The position statement reaffirms metformin as the preferred initial agent, barring contraindication or intolerance, either in addition to lifestyle counseling and support for weight loss and exercise, or when lifestyle efforts alone have not achieved or maintained glycemic goals. Metformin has a long-standing evidence base for efficacy and safety, is inexpensive, and may reduce risk of cardiovascular events (87). When metformin fails to achieve or maintain glycemic goals, another agent should be added. Although there are numerous trials comparing dual therapy to metformin alone, few directly compare drugs as add-on therapy. Comparative effectiveness meta-analyses (114) suggest that overall, each new class of noninsulin agents added to initial therapy lowers A1C around 0.9–1.1%.

Many patients with type 2 diabetes eventually require and benefit from insulin therapy. The progressive nature of type 2 diabetes and its therapies should be regularly and objectively explained to patients. Providers should avoid using insulin as a threat or describing it as a failure or punishment. Equipping patients with an algorithm for self-titration of insulin doses based on SMBG results improves glycemic control in type 2 diabetic patients initiating insulin (115). Refer to the ADA-EASD position statement for more details on pharmacotherapy for hyperglycemia in type 2 diabetes (113) (Fig. 2).

E. Medical Nutrition Therapy

General Recommendations

- Nutrition therapy is recommended for all people with type 1 and type 2 diabetes as an effective component of the overall treatment plan. **A**
- Individuals who have prediabetes or diabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of diabetes MNT. **A**
- Because diabetes nutrition therapy can result in cost savings **B** and improved outcomes such as reduction in A1C **A**, nutrition therapy should be adequately reimbursed by insurance and other payers. **E**

Energy Balance, Overweight, and Obesity

- For overweight or obese adults with type 2 diabetes or at risk for diabetes, reducing energy intake while maintaining a healthful eating pattern is recommended to promote weight loss. **A**
- Modest weight loss may provide clinical benefits (improved glycemia, blood pressure, and/or lipids) in some individuals with diabetes, especially those early in the disease process. To achieve modest weight loss, intensive lifestyle interventions (counseling about nutrition therapy, physical activity, and behavior change) with ongoing support are recommended. **A**

Eating Patterns and Macronutrient Distribution

- Evidence suggests that there is not an ideal percentage of calories from

carbohydrate, protein, and fat for all people with diabetes **B**; therefore, macronutrient distribution should be based on individualized assessment of current eating patterns, preferences, and metabolic goals. **E**

- A variety of eating patterns (combinations of different foods or food groups) are acceptable for the management of diabetes. Personal preference (e.g., tradition, culture, religion, health beliefs and goals, economics) and metabolic goals should be considered when recommending one eating pattern over another. **E**

Carbohydrate Amount and Quality

- Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains a key strategy in achieving glycemic control. **B**
- For good health, carbohydrate intake from vegetables, fruits, whole grains, legumes, and dairy products should be advised over intake from other carbohydrate sources, especially those that contain added fats, sugars, or sodium. **B**
- Substituting low-glycemic load foods for higher-glycemic load foods may modestly improve glycemic control. **C**
- People with diabetes should consume at least the amount of fiber and whole grains recommended for the general public. **C**
- While substituting sucrose-containing foods for isocaloric amounts of other carbohydrates may have similar blood glucose effects, consumption should be minimized to avoid displacing nutrient-dense food choices. **A**
- People with diabetes and those at risk for diabetes should limit or avoid intake of sugar-sweetened beverages (from any caloric sweetener including high-fructose corn syrup and sucrose) to reduce risk for weight gain and worsening of cardiometabolic risk profile. **B**

Dietary Fat Quantity and Quality

- Evidence is inconclusive for an ideal amount of total fat intake for people with diabetes; therefore, goals should be individualized. **C** Fat quality appears to be far more important than quantity. **B**

- In people with type 2 diabetes, a Mediterranean-style, MUFA-rich eating pattern may benefit glycemic control and CVD risk factors and can therefore be recommended as an effective alternative to a lower-fat, higher-carbohydrate eating pattern. **B**
- As recommended for the general public, an increase in foods containing long-chain n-3 fatty acids (EPA and DHA) (from fatty fish) and n-3 linolenic acid (ALA) is recommended for individuals with diabetes because of their beneficial effects on lipoproteins, prevention of heart disease, and associations with positive health outcomes in observational studies. **B**
- The amount of dietary saturated fat, cholesterol, and *trans* fat recommended for people with diabetes is the same as that recommended for the general population. **C**

Supplements for Diabetes Management

- There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes who do not have underlying deficiencies. **C**
- Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety. **A**
- Evidence does not support recommending n-3 (EPA and DHA) supplements for people with diabetes for the prevention or treatment of cardiovascular events. **A**
- There is insufficient evidence to support the routine use of micronutrients such as chromium, magnesium, and vitamin D to improve glycemic control in people with diabetes. **C**
- There is insufficient evidence to support the use of cinnamon or other herbs/supplements for the treatment of diabetes. **C**
- It is reasonable for individualized meal planning to include optimization of food choices to meet recommended daily allowance/dietary reference intake for all micronutrients. **E**

Alcohol

- If adults with diabetes choose to drink alcohol, they should be advised to do so in moderation (one drink per day or less for adult women and two drinks per day or less for adult men). **E**
- Alcohol consumption may place people with diabetes at increased risk for delayed hypoglycemia, especially if taking insulin or insulin secretagogues. Education and awareness regarding the recognition and management of delayed hypoglycemia is warranted. **C**

Sodium

- The recommendation for the general population to reduce sodium to <2,300 mg/day is also appropriate for people with diabetes. **B**
- For individuals with both diabetes and hypertension, further reduction in sodium intake should be individualized. **B**

Primary Prevention of Type 2 Diabetes

- Among individuals at high risk for developing type 2 diabetes, structured programs that emphasize lifestyle changes that include moderate weight loss (7% of body weight) and regular physical activity (150 min/week), with dietary strategies including reduced calories and reduced intake of dietary fat, can reduce the risk for developing diabetes and are therefore recommended. **A**
- Individuals at high risk for type 2 diabetes should be encouraged to achieve the U.S. Department of Agriculture (USDA) recommendation for dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain intake). **B**

The ADA recently released an updated position statement on nutrition therapy for adults living with diabetes (116). Nutrition therapy is an integral component of diabetes prevention, management, and self-management education. All individuals with diabetes should receive individualized MNT preferably provided by a registered dietitian who is knowledgeable and skilled in providing diabetes MNT. Comprehensive group diabetes education programs including nutrition

therapy or individualized education sessions have reported A1C decreases of 0.3–1% for type 1 diabetes (117–120) and 0.5–2% for type 2 diabetes (85,121–137).

Individuals with type 1 diabetes should be offered intensive insulin therapy education using the carbohydrate-counting meal planning approach (117,119,120,124,138–140); this approach has been shown to improve glycemic control (139,141). Consistent carbohydrate intake with respect to time and amount can result in improved glycemic control for individuals using fixed daily insulin doses (142,143). A simple diabetes meal planning approach such as portion control or healthful food choices may be better suited for individuals with health literacy and numeracy concerns (125–127).

Weight loss of 2–8 kg may provide clinical benefits in those with type 2 diabetes, especially early in the disease process (144–146). Weight loss studies have used a variety of energy-restricted eating patterns, with no clear evidence that one eating pattern or optimal macronutrient distribution was ideal. Although several studies resulted in improvements in A1C at 1 year (144,145,147–149), not all weight loss interventions led to 1-year A1C improvements (128,150–154). The most consistently identified changes in cardiovascular risk factors were an increase in HDL cholesterol (144,145, 147,149,153,155), decrease in triglycerides (144,145,149,155,156) and decrease in blood pressure (144,145,147,151,153,155).

Intensive lifestyle programs with frequent follow-up are required to achieve significant reductions in excess body weight and improve clinical indicators (145,146). Several studies have attempted to identify the optimal mix of macronutrients for meal plans of people with diabetes. However, a recent systematic review (157) found that there was no ideal macronutrient distribution and that macronutrient proportions should be individualized. Studies show that people with diabetes on average eat about 45% of their calories from carbohydrate, ~36–40% of calories from fat, and ~16–18% from

protein (158–160). A variety of eating patterns have been shown to be effective in managing diabetes, including Mediterranean-style (144,146,169), Dietary Approaches to Stop Hypertension (DASH)-style (161), plant-based (vegan or vegetarian) (129), lower-fat (145), and lower-carbohydrate patterns (144,163).

Studies examining the ideal amount of carbohydrate intake for people with diabetes are inconclusive, although monitoring carbohydrate intake and considering the available insulin are key strategies for improving postprandial glucose control (117,142,143,158). The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, although reductions in A1C of –0.2% to –0.5% have been demonstrated in some studies. In many studies, it is often difficult to discern the independent effect of fiber compared with that of glycemic index on glycemic control and other outcomes. Improvements in CVD risk measures are mixed (164). Recent studies have shown modest effect of fiber on lowering preprandial glucose and mixed results on improving CVD risk factors. A systematic review (157) found consumption of whole grains was not associated with improvements in glycemic control in people with type 2 diabetes, although it may reduce systemic inflammation. One study did find a potential benefit of whole grain intake in reducing mortality and CVD (165).

Limited research exists concerning the ideal amount of fat for individuals with diabetes. The Institute of Medicine has defined an acceptable macronutrient distribution range (AMDR) for all adults for total fat of 20–35% of energy with no tolerable upper intake level defined. This AMDR was based on evidence for CHD risk with a low intake of fat and high intake of carbohydrate, and evidence for increased obesity and CHD with high intake of fat (166). The type of fatty acids consumed is more important than total amount of fat when looking at metabolic goals and risk of CVD (146,167,168).

Multiple RCTs including patients with type 2 diabetes have reported improved

glycemic control and/or blood lipids when a Mediterranean-style, MUFA-rich eating pattern was consumed (144,146,151,169–171). Some of these studies also included caloric restriction, which may have contributed to improvements in glycemic control or blood lipids (169,170). The ideal ratio of n-6 to n-3 fatty acids has not been determined; however, PUFA and MUFA are recommended substitutes for saturated or *trans* fat (167,172).

A recent systematic review (157) concluded that supplementation with n-3 fatty acids did not improve glycemic control but that higher dose supplementation decreased triglycerides in individuals with type 2 diabetes. Six short-duration RCTs comparing n-3 supplements to placebo published since the systematic review reported minimal or no beneficial effects (173,174) or mixed/inconsistent beneficial effects (175–177) on CVD risk factors and other health issues. Three longer-duration studies also reported mixed outcomes (178–180). Thus, RCTs do not support recommending n-3 supplements for primary or secondary prevention of CVD. Little evidence has been published about the relationship between dietary intake of saturated fatty acids and dietary cholesterol and glycemic control and CVD risk in people with diabetes. Therefore, people with diabetes should follow the guidelines for the general population for the recommended intakes of saturated fat, dietary cholesterol, and *trans* fat (167). Published data on the effects of plant stanols and sterols on CVD risk in individuals with diabetes include four RCTs that reported beneficial effects for total, LDL, and non-HDL cholesterol (181–184).

There is limited evidence that the use of vitamin, mineral, or herbal supplements is necessary in the management of diabetes (185–201).

Limited studies have been published on sodium reduction in people with diabetes. A recent Cochrane review found that decreasing sodium intake reduces blood pressure in those with diabetes (202). However, two other studies in type 1 diabetes (203) and type

2 diabetes (204) have warranted caution for universal sodium restriction to 1,500 mg in this population. For individuals with diabetes and hypertension, setting a sodium intake goal of <2,300 mg/day should be considered only on an individual basis. Goal sodium intake recommendations should take into account palatability, availability, additional cost of specialty low sodium products, and the difficulty of achieving both low sodium recommendations and a nutritionally adequate diet (205). For complete discussion and references of all recommendations, see “Nutrition Therapy Recommendations for the Management of Adults With Diabetes” (116).

F. Diabetes Self-Management Education and Support

Recommendations

- People with diabetes should receive DSME and diabetes self-management support (DSMS) according to National Standards for Diabetes Self-Management Education and Support when their diabetes is diagnosed and as needed thereafter. **B**
- Effective self-management and quality of life are the key outcomes of DSME and DSMS and should be measured and monitored as part of care. **C**
- DSME and DSMS should address psychosocial issues, since emotional well-being is associated with positive diabetes outcomes. **C**
- DSME and DSMS programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. **C**
- Because DSME and DSMS can result in cost-savings and improved outcomes **B**, DSME and DSMS should be adequately reimbursed by third-party payers. **E**

DSME and DSMS are the ongoing processes of facilitating the knowledge, skill, and ability necessary for diabetes self-care. This process incorporates the needs, goals, and life experiences of the person with diabetes. The overall objectives of DSME and DSMS are to support informed decision making, self-care behaviors, problem solving, and active collaboration with the health care

team to improve clinical outcomes, health status, and quality of life in a cost-effective manner (206).

DSME and DSMS are essential elements of diabetes care (207–209), and the current National Standards for Diabetes Self-Management Education and Support (206) are based on evidence for their benefits. Education helps people with diabetes initiate effective self-management and cope with diabetes when they are first diagnosed. Ongoing DSME and DSMS also help people with diabetes maintain effective self-management throughout a lifetime of diabetes as they face new challenges and treatment advances become available. DSME enables patients (including youth) to optimize metabolic control, prevent and manage complications, and maximize quality of life, in a cost-effective manner (208,210).

Current best practice of DSME is a skills-based approach that focuses on helping those with diabetes make informed self-management choices (206,208). DSME has changed from a didactic approach focusing on providing information to more theoretically based empowerment models that focus on helping those with diabetes make informed self-management decisions (208). Diabetes care has shifted to an approach that is more patient centered and places the person with diabetes and his or her family at the center of the care model working in collaboration with health care professionals. Patient-centered care is respectful of and responsive to individual patient preferences, needs, and values and ensures that patient values guide all decision making (211).

Evidence for the Benefits of Diabetes Self-Management Education and Support

Multiple studies have found that DSME is associated with improved diabetes knowledge and improved self-care behavior (206,207), improved clinical outcomes such as lower A1C (209,212–216), lower self-reported weight (207), improved quality of life (213,216,217), healthy coping (218,219), and lower costs (220,221). Better outcomes were reported for DSME interventions that were longer and included follow-up support (DSMS) (207,222–224), that

were culturally (225,226) and age appropriate (227,228) and were tailored to individual needs and preferences, and that addressed psychosocial issues and incorporated behavioral strategies (207,208,218,219,229–231). Both individual and group approaches have been found effective (232,233). There is growing evidence for the role of a community health workers (234) and peer (235–239) and lay leaders (240) in delivering DSME and DSMS as part of the DSME/S team (241).

Diabetes education is associated with increased use of primary and preventive services (220,242,243) and lower use of acute, inpatient hospital services (220). Patients who participate in diabetes education are more likely to follow best practice treatment recommendations, particularly among the Medicare population, and have lower Medicare and commercial claim costs (221,242).

The National Standards for Diabetes Self-Management Education and Support

The National Standards for Diabetes Self-Management Education and Support are designed to define quality DSME and DSMS and to assist diabetes educators in a variety of settings to provide evidence-based education and self-management support (206). The standards are reviewed and updated every 5 years by a task force representing key organizations involved in the field of diabetes education and care.

Diabetes Self-Management Education and Support Providers and People With Prediabetes

The standards for DSME and DSMS also apply to the education and support of people with prediabetes. Currently, there are significant barriers to the provision of education and support to those with prediabetes. However, the strategies for supporting successful behavior change and the healthy behaviors recommended for people with prediabetes are largely identical to those for people with diabetes. As barriers to care are overcome, providers of DSME and DSMS, given their training and experience, are particularly well equipped to assist people with prediabetes in developing and maintaining behaviors that can prevent or delay the onset of diabetes (206,244,245).

Reimbursement for Diabetes Self-Management Education and Support DSME, when provided by a program that meets national standards for DSME and is recognized by ADA or other approval bodies, is reimbursed as part of the Medicare program as overseen by the Centers for Medicare and Medicaid Services (CMS). DSME is also covered by most health insurance plans.

Although DSMS has been shown to be instrumental for improving outcomes, as described in “Evidence for the Benefits of Diabetes Self-Management Education and Support,” and can be provided in formats such as phone calls and via telehealth, it currently has limited reimbursement as face-to-face visits included as follow-up to DSME.

G. Physical Activity

Recommendations

- As is the case for all children, children with diabetes or prediabetes should be encouraged to engage in at least 60 min of physical activity each day. **B**
- Adults with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise. **A**
- In the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week. **A**

Exercise is an important part of the diabetes management plan. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals (23–25). Structured exercise interventions of at least 8 weeks’ duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even with no significant change in BMI (246). There are considerable data for the health benefits (e.g., increased cardiovascular fitness, muscle strength, improved insulin sensitivity, etc.) of regular physical activity for those with type 1 diabetes (247). Higher levels of exercise intensity are associated with greater

improvements in A1C and in fitness (248). Other benefits include slowing the decline in mobility among overweight patients with diabetes (249). A joint position statement of ADA and the American College of Sports Medicine summarizes the evidence for the benefits of exercise in people with type 2 diabetes (250).

Frequency and Type of Exercise

The U.S. Department of Health and Human Services’ Physical Activity Guidelines for Americans (251) suggest that adults over age 18 years do 150 min/week of moderate-intensity, or 75 min/week of vigorous aerobic physical activity, or an equivalent combination of the two. In addition, the guidelines suggest that adults also do muscle-strengthening activities that involve all major muscle groups 2 or more days/week. The guidelines suggest that adults over age 65 years, or those with disabilities, follow the adult guidelines if possible or (if this is not possible) be as physically active as they are able. Studies included in the meta-analysis of effects of exercise interventions on glycemic control (246) had a mean of 3.4 sessions/week, with a mean of 49 min/session. The DPP lifestyle intervention, which included 150 min/week of moderate-intensity exercise, had a beneficial effect on glycemia in those with prediabetes. Therefore, it seems reasonable to recommend that people with diabetes follow the physical activity guidelines for the general population.

Progressive resistance exercise improves insulin sensitivity in older men with type 2 diabetes to the same or even a greater extent as aerobic exercise (252). Clinical trials have provided strong evidence for the A1C lowering value of resistance training in older adults with type 2 diabetes (253,254), and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (255,256). In the absence of contraindications, patients with type 2 diabetes should be encouraged to do at least two weekly sessions of resistance exercise (exercise with free weights or weight machines), with each session consisting of at least one set of five or

more different resistance exercises involving the large muscle groups (250).

Pre-exercise Evaluation of the Diabetic Patient

As discussed more fully in Section VI.A.5, the area of screening asymptomatic diabetic patients for coronary artery disease (CAD) remains unclear. An ADA consensus statement on this issue concluded that routine screening is not recommended (257). Providers should use clinical judgment in this area. Certainly, high-risk patients should be encouraged to start with short periods of low-intensity exercise and increase the intensity and duration slowly. Providers should assess patients for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, severe autonomic neuropathy, severe peripheral neuropathy or history of foot lesions, and unstable proliferative retinopathy. The patient's age and previous physical activity level should be considered. For type 1 diabetic patients, the provider should customize the exercise regimen to the individual's needs. Those with complications may require a more thorough evaluation (247).

Exercise in the Presence of Nonoptimal Glycemic Control

Hyperglycemia. When people with type 1 diabetes are deprived of insulin for 12–48 h and are ketotic, exercise can worsen hyperglycemia and ketosis (258); therefore, vigorous activity should be avoided in the presence of ketosis. However, it is not necessary to postpone exercise based simply on hyperglycemia, provided the patient feels well and urine and/or blood ketones are negative.

Hypoglycemia. In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycemia if medication dose or carbohydrate consumption is not altered. For individuals on these therapies, added carbohydrate should be ingested if pre-exercise glucose levels are <100 mg/dL (5.6 mmol/L). Hypoglycemia is less common in diabetic individuals who are not treated with insulin or insulin secretagogues, and no preventive measures for hypoglycemia are usually advised in these cases.

Exercise in the Presence of Specific Long-Term Complications of Diabetes

Retinopathy. In the presence of proliferative diabetic retinopathy (PDR) or severe non-PDR (NPDR), vigorous aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (259).

Peripheral Neuropathy. Decreased pain sensation and a higher pain threshold in the extremities result in increased risk of skin breakdown and infection and of Charcot joint destruction with some forms of exercise. However, studies have shown that moderate-intensity walking may not lead to increased risk of foot ulcers or reulceration in those with peripheral neuropathy (260). In addition, 150 min/week of moderate exercise was reported to improve outcomes in patients with milder forms of neuropathy (260a). All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non-weight-bearing activities.

Autonomic Neuropathy. Autonomic neuropathy can increase the risk of exercise-induced injury or adverse event through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and higher susceptibility to hypoglycemia (454). Cardiovascular autonomic neuropathy (CAN) is also an independent risk factor for cardiovascular death and silent myocardial ischemia (261). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Albuminuria and Nephropathy. Physical activity can acutely increase urinary protein excretion. However, there is no evidence that vigorous exercise increases the rate of progression of diabetic kidney disease and likely no need for any specific exercise restrictions for people with diabetic kidney disease (262).

H. Psychosocial Assessment and Care Recommendations

- It is reasonable to include assessment of the patient's psychological and social situation as an ongoing part of the medical management of diabetes. **B**
- Psychosocial screening and follow-up may include, but are not limited to, attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social, and emotional), and psychiatric history. **E**
- Routinely screen for psychosocial problems such as depression and diabetes-related distress, anxiety, eating disorders, and cognitive impairment. **B**

Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's (263–265) or family's ability (266) to carry out diabetes care tasks and therefore compromise health status. There are opportunities for the clinician to routinely assess psychosocial status in a timely and efficient manner so that referral for appropriate services can be accomplished. A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C (standardized mean difference -0.29%) and mental health outcomes. However, there was a limited association between the effects on A1C and mental health, and no intervention characteristics predicted benefit on both outcomes (267).

Screening

Key opportunities for routine screening of psychosocial status occur at diagnosis, during regularly scheduled management visits, during hospitalizations, with the discovery of complications, or when problems with glucose control, quality of life, or self-management are identified. Patients are likely to exhibit psychological vulnerability at diagnosis and when their medical status changes, e.g., end of the honeymoon period, when the need for intensified treatment is evident, and when complications are discovered. Depression affects about 20–25% of people with diabetes (268) and increases the risk for MI and post-MI (269) and

all-cause mortality (270). There appears to be a bidirectional relationship with both diabetes (271) and metabolic syndrome (272) and depression.

Diabetes-related distress is distinct from clinical depression and is very common (273–276) among people with diabetes and their family members (266). Prevalence is reported as 18–45%, with an incidence of 38–48% over 18 months. High levels of distress are significantly linked to A1C, self-efficacy, dietary and exercise behaviors (219,274), and medication taking (277). Other issues known to impact self-management and health outcomes include but are not limited to attitudes about the illness, expectations for medical management and outcomes, anxiety, general and diabetes-related quality of life, resources (financial, social, and emotional) (278) and psychiatric history (279,280). Screening tools are available for a number of these areas (229,281,282).

Referral to Mental Health Specialist

Indications for referral to a mental health specialist familiar with diabetes management may include gross disregard for the medical regimen (by self or others) (283), depression, possibility of self-harm, debilitating anxiety (alone or with depression), indications of an eating disorder (284), or cognitive functioning that significantly impairs judgment. It is preferable to incorporate psychological assessment and treatment into routine care rather than waiting for a specific problem or deterioration in metabolic or psychological status (229,273). In the recent DAWN2 study, significant diabetes-related distress was reported by 44.6% of the participants, but only 23.7% reported that their health care team asked them how diabetes impacted their life (273).

Although the clinician may not feel qualified to treat psychological problems (285), using the patient-provider relationship as a foundation can increase the likelihood that the patient will accept referral for other services. Collaborative care interventions and use of a team approach have demonstrated efficacy in diabetes and depression (286,287), and

interventions to enhance self-management and address severe distress have demonstrated efficacy in diabetes-related distress (219).

I. When Treatment Goals Are Not Met

Some people with diabetes and their health care providers may not achieve the desired treatment goals (Table 9). Rethinking the treatment regimen may require assessment of barriers including income, health literacy, diabetes-related distress, depression, and competing demands, including those related to family responsibilities and dynamics. Other strategies may include culturally appropriate and enhanced DSME and DSMS, comanagement with a diabetes team, referral to a medical social worker for assistance with insurance coverage, assessing medication-taking behaviors, or change in pharmacological therapy. Initiation of or increase in SMBG, use of CGM, frequent contact with the patient, or referral to a mental health professional or physician with special expertise in diabetes may be useful.

J. Intercurrent Illness

The stress of illness, trauma, and/or surgery frequently aggravates glycemic control and may precipitate DKA or nonketotic hyperosmolar state, life-threatening conditions that require immediate medical care to prevent complications and death. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose and (in ketosis-prone patients) urine or blood ketones. If accompanied by ketosis, vomiting, or alteration in level of consciousness, marked hyperglycemia requires temporary adjustment of the treatment regimen and immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or MNT alone may temporarily require insulin. Adequate fluid and caloric intake must be assured. Infection or dehydration is more likely to necessitate hospitalization of the person with diabetes than the person without diabetes.

The hospitalized patient should be treated by a physician with expertise in diabetes management. For further information on management of patients

with hyperglycemia in the hospital, see Section IX.A. For further information on management of DKA or hyperglycemic nonketotic hyperosmolar state, refer to the ADA statement on hyperglycemic crises (288).

K. Hypoglycemia

Recommendations

- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. **C**
- Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia, although any form of carbohydrate that contains glucose may be used. After 15 min of treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **E**
- Glucagon should be prescribed for all individuals at significant risk of severe hypoglycemia, and caregivers or family members of these individuals should be instructed on its administration. Glucagon administration is not limited to health care professionals. **E**
- Hypoglycemia unawareness or one or more episodes of severe hypoglycemia should trigger re-evaluation of the treatment regimen. **E**
- Insulin-treated patients with hypoglycemia unawareness or an episode of severe hypoglycemia should be advised to raise their glycemic targets to strictly avoid further hypoglycemia for at least several weeks, to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**
- Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition and/or declining cognition is found. **B**

Hypoglycemia is the leading limiting factor in the glycemic management of type 1 and insulin-treated type 2 diabetes (289). Mild hypoglycemia may be inconvenient or frightening to patients with diabetes. Severe

hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury. A large cohort study suggested that among older adults with type 2 diabetes, a history of severe hypoglycemia was associated with greater risk of dementia (290). Conversely, in a substudy of the ACCORD trial, cognitive impairment at baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of severe hypoglycemia (291). Evidence from the DCCT/EDIC trial, which involved younger adults and adolescents with type 1 diabetes, suggested no association of frequency of severe hypoglycemia with cognitive decline (292), as discussed in Section VIII.A.1.a.

As described in Section V.b.2, severe hypoglycemia was associated with mortality in participants in both the standard and intensive glycemia arms of the ACCORD trial, but the relationships with achieved A1C and treatment intensity were not straightforward. An association of severe hypoglycemia with mortality was also found in the ADVANCE trial (293). An association of self-reported severe hypoglycemia with 5-year mortality has also been reported in clinical practice (294).

In 2013, ADA and The Endocrine Society published a consensus report on the impact and treatment of hypoglycemia on diabetic patients. Severe hypoglycemia was defined as an event requiring assistance of another person. Young children with type 1 diabetes and the elderly were noted as particularly vulnerable due to their limited ability to recognize hypoglycemic symptoms and effectively communicate their needs. The report recommended that short-acting insulin sliding scales, often used in long-term care facilities, should be avoided and complex regimens simplified. Individualized patient education, dietary intervention (e.g., bedtime snack to prevent overnight hypoglycemia), exercise management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes (295).

Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content than with the carbohydrate content of the food. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless further food is ingested after recovery.

Glucagon

Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, child care providers, correctional institution staff, or coworkers) should be instructed on use of glucagon kits. An individual does not need to be a health care professional to safely administer glucagon. A glucagon kit requires a prescription. Care should be taken to ensure that glucagon kits are not expired.

Hypoglycemia Prevention

Hypoglycemia prevention is a critical component of diabetes management. SMBG and, for some patients, CGM are key tools to assess therapy and detect incipient hypoglycemia. Patients should understand situations that increase their risk of hypoglycemia, such as when fasting for tests or procedures, during or after intense exercise, and during sleep, and that hypoglycemia may increase the risk of harm to self or others, such as with driving. Teaching people with diabetes to balance insulin use, carbohydrate intake, and exercise is a necessary but not always sufficient strategy for prevention. In type 1 diabetes and severely insulin-deficient type 2 diabetes, hypoglycemia unawareness, or hypoglycemia-associated autonomic failure, can severely compromise stringent diabetes control and quality of life. The deficient counter-regulatory hormone release and autonomic responses in this syndrome are both risk factors for, and caused by, hypoglycemia. A corollary to this “vicious cycle” is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counter-regulation and awareness to some extent in many

patients (296). Hence, patients with one or more episodes of severe hypoglycemia may benefit from at least short-term relaxation of glycemic targets.

L. Bariatric Surgery

Recommendations

- Bariatric surgery may be considered for adults with BMI >35 kg/m² and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. **B**
- Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring. **B**
- Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m², there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m² outside of a research protocol. **E**
- The long-term benefits, cost-effectiveness, and risks of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed controlled trials with optimal medical and lifestyle therapy as the comparator. **E**

Bariatric and metabolic surgeries, either gastric banding or procedures that involve bypassing, transposing, or resecting sections of the small intestine, when part of a comprehensive team approach, can be an effective weight loss treatment for severe obesity, and national guidelines support its consideration for people with type 2 diabetes who have BMI exceeding 35 kg/m².

Advantages

Bariatric surgery has been shown to lead to near- or complete normalization of glycemia in ~40–95% of patients with type 2 diabetes, depending on the study and the surgical procedure (297–300). A meta-analysis of bariatric surgery studies involving 3,188 patients with diabetes reported that 78% had remission of diabetes (normalization of blood glucose levels in the absence of medications) and that the remission rates were sustained in studies that had follow-up exceeding 2 years (301). Remission rates tend to be lower with procedures that only constrict the

stomach and higher with those that bypass portions of the small intestine. Additionally, intestinal bypass procedures may have glycemic effects that are independent of their effects on weight, perhaps involving the incretin axis.

There is also evidence for diabetes remission following bariatric surgery in persons with type 2 diabetes who are less severely obese. One randomized trial compared adjustable gastric banding to “best available” medical and lifestyle therapy in subjects with type 2 diabetes and BMI 30–40 kg/m² (302). Overall, 73% of surgically treated patients achieved “remission” of their diabetes, compared with 13% of those treated medically. The latter group lost only 1.7% of body weight, suggesting that their therapy was not optimal. Overall the trial had 60 subjects, and only 13 had a BMI under 35 kg/m², making it difficult to generalize these results widely to diabetic patients who are less severely obese or with longer duration of diabetes. In a recent nonrandomized study of 66 people with BMI 30–35 kg/m², 88% of participants had remission of their type 2 diabetes up to 6 years after surgery (303).

Disadvantages

Bariatric surgery is costly in the short term and has associated risks. Morbidity and mortality rates directly related to the surgery have been reduced considerably in recent years, with 30-day mortality rates now 0.28%, similar to those of laparoscopic cholecystectomy (304). Longer-term concerns include vitamin and mineral deficiencies, osteoporosis, and rare but often severe hypoglycemia from insulin hypersecretion. Cohort studies attempting to match subjects suggest that the procedure may reduce longer-term mortality rates (305). Retrospective analyses and modeling studies suggest that these procedures may be cost-effective for patients with type 2 diabetes, when one considers reduction in subsequent health care costs (297,306–308).

Caution about the benefits of bariatric surgery is warranted. A propensity score-adjusted analyses of older severely obese patients with high baseline mortality in Veterans Affairs Medical Centers found that bariatric surgery was not associated with

decreased mortality compared with usual care (mean follow-up 6.7 years) (309). A study that followed patients who had undergone laparoscopic adjustable gastric banding (LAGB) for 12 years found that 60% were satisfied with the procedure. Nearly one out of three patients experienced band erosion, and almost half had required removal of their bands. The authors' conclusion was that “LAGB appears to result in relatively poor long-term outcomes” (310). Understanding the mechanisms of glycemic improvement, long-term benefits, and risks of bariatric surgery in individuals with type 2 diabetes, especially those who are not severely obese, will require well designed clinical trials, with optimal medical and lifestyle therapy, and cardiovascular risk factors as the comparator.

M. Immunization

Recommendations

- Annually provide an influenza vaccine to all diabetic patients ≥ 6 months of age. **C**
- Administer pneumococcal polysaccharide vaccine to all diabetic patients ≥ 2 years of age. A one-time revaccination is recommended for individuals > 65 years of age who have been immunized > 5 years ago. Other indications for repeat vaccination include nephrotic syndrome, chronic renal disease, and other immunocompromised states, such as after transplantation. **C**
- Administer hepatitis B vaccination to unvaccinated adults with diabetes who are aged 19–59 years. **C**
- Consider administering hepatitis B vaccination to unvaccinated adults with diabetes who are aged ≥ 60 years. **C**

Influenza and pneumonia are common, preventable infectious diseases associated with high mortality and morbidity in the elderly and in people with chronic diseases. Though there are limited studies reporting the morbidity and mortality of influenza and pneumococcal pneumonia specifically in people with diabetes, observational studies of patients with a variety of chronic illnesses, including diabetes, show that these conditions are associated with an increase in

hospitalizations for influenza and its complications. People with diabetes may be at increased risk of the bacteremic form of pneumococcal infection and have been reported to have a high risk of nosocomial bacteremia, which has a mortality rate as high as 50% (311).

Safe and effective vaccines that greatly reduce the risk of serious complications from these diseases are available (312,313). In a case-control series, influenza vaccine was shown to reduce diabetes-related hospital admission by as much as 79% during flu epidemics (312). There is sufficient evidence to support that people with diabetes have appropriate serologic and clinical responses to these vaccinations. The CDC Advisory Committee on Immunization Practices recommends influenza and pneumococcal vaccines for all individuals with diabetes (<http://www.cdc.gov/vaccines/recs/>).

Hepatitis B Vaccine

Late in 2012, the Advisory Committee on Immunization Practices of the CDC recommended that all previously unvaccinated adults with diabetes aged 19–59 years be vaccinated against hepatitis B virus (HBV) as soon as possible after a diagnosis of diabetes is made. Additionally, after assessing risk and likelihood of an adequate immune response, vaccinations for those aged 60 years and over should also be considered (314). At least 29 outbreaks of HBV in long-term care facilities and hospitals have been reported to the CDC, with the majority involving adults with diabetes receiving “assisted blood glucose monitoring,” in which such monitoring is done by a health care professional with responsibility for more than one patient. HBV is highly transmissible and stable for long periods of time on surfaces such as lancing devices and blood glucose meters, even when no blood is visible. Blood sufficient to transmit the virus has also been found in the reservoirs of insulin pens, resulting in warnings against sharing such devices between patients.

CDC analyses suggest that, excluding persons with HBV-related risk behaviors, acute HBV infection is about twice as high among adults with

diabetes aged 23 years and over compared with adults without diabetes. Seroprevalence of antibody to HBV core antigen, suggesting past or current infection, is 60% higher among adults with diabetes than those without, and there is some evidence that diabetes imparts a higher HBV case fatality rate. The age differentiation in the recommendations stems from CDC economic models suggesting that vaccination of adults with diabetes who were aged 20–59 years would cost an estimated \$75,000 per quality-adjusted life-year saved, while cost per quality-adjusted life-year saved increased significantly at higher ages. In addition to competing causes of mortality in older adults, the immune response to the vaccine declines with age (314).

These new recommendations regarding HBV vaccinations serve as a reminder to clinicians that children and adults with diabetes need a number of vaccinations, both those specifically indicated because of diabetes as well as those recommended for the general population (<http://www.cdc.gov/vaccines/recs/>).

VI. PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

For prevention and management of diabetes complications in children and adolescents, please refer to Section VIII. Diabetes Care in Specific Populations.

A. Cardiovascular Disease

CVD is the major cause of morbidity and mortality for individuals with diabetes, and the largest contributor to the direct and indirect costs of diabetes. The common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for CVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing CVD in people with diabetes. Large benefits are seen when multiple risk factors are addressed globally (315,316). There is evidence that measures of 10-year CHD risk among U.S. adults with diabetes have improved significantly over the past decade (317).

1. Hypertension/Blood Pressure Control

Recommendations

Screening and Diagnosis

- Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. **B**

Goals

- People with diabetes and hypertension should be treated to a systolic blood pressure (SBP) goal of <140 mmHg. **B**
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. **C**
- Patients with diabetes should be treated to a diastolic blood pressure (DBP) <80 mmHg. **B**

Treatment

- Patients with blood pressure >120/80 mmHg should be advised on lifestyle changes to reduce blood pressure. **B**
- Patients with confirmed blood pressure higher than 140/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. **B**
- Lifestyle therapy for elevated blood pressure consists of weight loss, if overweight; DASH-style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. **B**
- Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted. **C**
- Multiple-drug therapy (two or more agents at maximal doses) is generally required to achieve blood pressure targets. **B**
- Administer one or more antihypertensive medications at bedtime. **A**
- If ACE inhibitors, ARBs, or diuretics are used, serum creatinine/estimated glomerular filtration rate (eGFR) and serum potassium levels should be monitored. **E**

- In pregnant patients with diabetes and chronic hypertension, blood pressure target goals of 110–129/65–79 mmHg are suggested in the interest of long-term maternal health and minimizing impaired fetal growth. ACE inhibitors and ARBs are contraindicated during pregnancy. **E**

Hypertension is a common comorbidity of diabetes, affecting the majority of patients, with prevalence depending on type of diabetes, age, obesity, and ethnicity. Hypertension is a major risk factor for both CVD and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying nephropathy, while in type 2 diabetes it usually coexists with other cardiometabolic risk factors.

Screening and Diagnosis

Blood pressure measurement should be done by a trained individual and follow the guidelines established for nondiabetic individuals: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper arm circumference. Elevated values should be confirmed on a separate day.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide additional evidence of “white coat” and masked hypertension and other discrepancies between office and “true” blood pressure. Studies in nondiabetic populations found that home measurements may better correlate with CVD risk than office measurements (318,319). However, most of the evidence of benefits of hypertension treatment in people with diabetes is based on office measurements.

Treatment Goals

Epidemiological analyses show that blood pressures >115/75 mmHg are associated with increased cardiovascular event rates and mortality in individuals with diabetes (320–322) and that SBP >120 mmHg predict long-term end-stage renal disease (ESRD). Randomized clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering blood pressure to <140 mmHg systolic and <80 mmHg diastolic in individuals with diabetes

(320,323–325). There is limited evidence for the benefits of lower SBP targets.

The ACCORD trial examined whether a lower SBP of <120 mmHg provides greater cardiovascular protection than an SBP level of 130–140 mmHg in patients with type 2 diabetes at high risk for CVD (326). The HR for the primary end point (nonfatal MI, nonfatal stroke, and CVD death) in the intensive (blood pressure 11/64 on 3.4 medications) versus standard group (blood pressure 143/70 on 2.1 medications) was 0.88 (95% CI 0.73–1.06; $P = 0.20$). Of the prespecified secondary end points, only stroke and nonfatal stroke were statistically significantly reduced by intensive blood pressure treatment. The number needed to treat to prevent one stroke over the course of 5 years with intensive blood pressure management was 89. Serious adverse event rates (including syncope and hyperkalemia) were higher with intensive targets (3.3% vs. 1.3%; $P = 0.001$). Albuminuria rates were reduced with more intensive blood pressure goals, but there were no differences in renal function nor in other microvascular complications.

The ADVANCE trial (treatment with an ACE inhibitor and a thiazide-type diuretic) showed a reduced death rate but not in the composite macrovascular outcome. However, the ADVANCE trial had no specified targets for the randomized comparison and the mean SBP in the intensive group (135 mmHg) was not as low as the mean SBP even in the ACCORD standard-therapy group (327). Post hoc analysis of achieved blood pressure in several hypertension treatment trials have suggested no benefit of lower achieved SBP. As an example, among 6,400 patients with diabetes and CAD enrolled in one trial, “tight control” (achieved SBP <130 mmHg) was not associated with improved cardiovascular outcomes compared with “usual care” (achieved SBP 130–140 mmHg) (328). Similar findings emerged from an analysis of another trial. Those with SBP (<115 mmHg) had increased rates of CVD events, although they had lower rates of stroke (329).

Observational data, including that derived from clinical trials, may be

inappropriate for defining blood pressure targets, since sicker patients may have low blood pressures or, conversely, healthier or more adherent patients may achieve goals more readily. A recent meta-analysis of randomized trials of adults with type 2 diabetes comparing prespecified blood pressure targets found no significant reduction in mortality or nonfatal MI. There was a statistically significant 35% relative reduction in stroke, but the absolute risk reduction was only 1% (330). Microvascular complications were not examined. Another meta-analysis that included both trials comparing blood pressure goals and trials comparing treatment strategies concluded that a systolic treatment goal of 130–135 mmHg was acceptable. With goals <130 mmHg, there were greater reductions in stroke, a 10% reduction in mortality, but no reduction of other CVD events and increased rates of serious adverse events. SBP <130 mmHg was associated with reduced onset and progression of albuminuria. However, there was heterogeneity in the measure, rates of more advanced renal disease outcomes were not affected, and there were no significant changes in retinopathy or neuropathy (331).

The clear body of evidence that SBP >140 mmHg is harmful suggests that clinicians should promptly initiate and titrate therapy in an ongoing fashion to achieve and maintain SBP <140 mmHg in virtually all patients. Additionally, patients with long life expectancy (in whom there may be renal benefits from long-term stricter blood pressure control) or those in whom stroke risk is a concern might, as part of shared decision making, appropriately have lower systolic targets such as <130 mmHg. This is especially true if it can be achieved with few drugs and without side effects of therapy.

Treatment Strategies

Although there are no well-controlled studies of diet and exercise in the treatment of elevated blood pressure or hypertension in individuals with diabetes, the DASH study in nondiabetic individuals has shown antihypertensive effects similar to pharmacological monotherapy. Lifestyle therapy consists

of reducing sodium intake (<1,500 mg/day) and excess body weight; increasing consumption of fruits, vegetables (8–10 servings per day), and low-fat dairy products (2–3 servings per day); avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (332); and increasing activity levels (320). These nonpharmacological strategies may also positively affect glycemia and lipid control and as a result should be encouraged in those with even mildly elevated blood pressure. Their effects on cardiovascular events have not been established. Nonpharmacological therapy is reasonable in diabetic individuals with mildly elevated blood pressure (SBP >120 mmHg or DBP >80 mmHg). If the blood pressure is confirmed to be ≥ 140 mmHg systolic and/or ≥ 80 mmHg diastolic, pharmacological therapy should be initiated along with nonpharmacological therapy (320).

Lowering of blood pressure with regimens based on a variety of antihypertensive drugs, including ACE inhibitors, ARBs, β -blockers, diuretics, and calcium channel blockers, has been shown to be effective in reducing cardiovascular events. Several studies suggested that ACE inhibitors may be superior to dihydropyridine calcium channel blockers in reducing cardiovascular events (333–335). However, several studies have shown no specific advantage to ACE inhibitors as initial treatment of hypertension in the general hypertensive population, but rather an advantage on cardiovascular outcomes of initial therapy with low-dose thiazide diuretics (320,336,337).

In people with diabetes, inhibitors of the renin-angiotensin system (RAS) may have unique advantages for initial or early therapy of hypertension. In a nonhypertension trial of high-risk individuals, including a large subset with diabetes, an ACE inhibitor reduced CVD outcomes (338). In patients with congestive heart failure (CHF), including diabetic subgroups, ARBs have been shown to reduce major CVD outcomes (339–342), and in type 2 diabetic patients with significant nephropathy, ARBs were superior to calcium channel

blockers for reducing heart failure (343). Though evidence for distinct advantages of RAS inhibitors on CVD outcomes in diabetes remains conflicting (323,337), the high CVD risks associated with diabetes, and the high prevalence of undiagnosed CVD, may still favor recommendations for their use as first-line hypertension therapy in people with diabetes (320).

The blood pressure arm of the ADVANCE trial demonstrated that routine administration of a fixed combination of the ACE inhibitor perindopril and the diuretic indapamide significantly reduced combined microvascular and macrovascular outcomes, as well as CVD and total mortality. The improved outcomes could also have been due to lower achieved blood pressure in the perindopril-indapamide arm (327). Another trial showed a decrease in morbidity and mortality in those receiving benazepril and amlodipine versus benazepril and hydrochlorothiazide (HCTZ). The compelling benefits of RAS inhibitors in diabetic patients with albuminuria or renal insufficiency provide additional rationale for these agents (see Section VI.B). If needed to achieve blood pressure targets, amlodipine, HCTZ, or chlorthalidone can be added. If eGFR is <30 mL/min/m², a loop diuretic, rather than HCTZ or chlorthalidone should be prescribed. Titration of and/or addition of further blood pressure medications should be made in timely fashion to overcome clinical inertia in achieving blood pressure targets.

Health information technology potentially can be used as a safe and effective tool to enable attainment of blood pressure goals. Using a telemonitoring intervention to direct titrations of antihypertensive medications between medical office visits has been demonstrated to have a profound impact on SBP control (344).

An important caveat is that most patients with hypertension require multiple-drug therapy to reach treatment goals (320). Identifying and addressing barriers to medication adherence (such as cost and side effects) should routinely be done. If blood pressure is refractory despite

confirmed adherence to optimal doses of at least three antihypertensive agents of different classifications, one of which should be a diuretic, clinicians should consider an evaluation for secondary forms of hypertension. Growing evidence suggests that there is an association between increase in sleep-time blood pressure and incidence of CVD events. A recent RCT of 448 participants with type 2 diabetes and hypertension demonstrated reduced cardiovascular events and mortality with median follow-up of 5.4 years if at least one antihypertensive medication was given at bedtime (345).

Pregnancy and Antihypertensives

In a pregnancy complicated by diabetes and chronic hypertension, target blood pressure goals of SBP 110–129 mmHg and DBP 65–79 mmHg are reasonable, as they contribute to improved long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they may cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (346).

2. Dyslipidemia/Lipid Management

Recommendations

Screening

- In most adult patients with diabetes, measure fasting lipid profile at least annually. **B**
- In adults with low-risk lipid values (LDL cholesterol <100 mg/dL, HDL cholesterol >50 mg/dL, and triglycerides <150 mg/dL), lipid assessments may be repeated every 2 years. **E**

Treatment Recommendations and Goals

- Lifestyle modification focusing on the reduction of saturated fat, *trans* fat, and cholesterol intake; increase of n-3 fatty acids, viscous fiber and plant stanols/sterols; weight loss (if indicated); and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. **A**

- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients:

- with overt CVD **A**
- without CVD who are over the age of 40 years and have one or more other CVD risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). **A**
- For lower-risk patients than the above (e.g., without overt CVD and under the age of 40 years), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains above 100 mg/dL or in those with multiple CVD risk factors. **C**
- In individuals without overt CVD, the goal is LDL cholesterol <100 mg/dL (2.6 mmol/L). **B**
- In individuals with overt CVD, a lower LDL cholesterol goal of <70 mg/dL (1.8 mmol/L), with a high dose of a statin, is an option. **B**
- If drug-treated patients do not reach the above targets on maximum tolerated statin therapy, a reduction in LDL cholesterol of ~ 30 – 40% from baseline is an alternative therapeutic goal. **B**
- Triglyceride levels <150 mg/dL (1.7 mmol/L) and HDL cholesterol >40 mg/dL (1.0 mmol/L) in men and >50 mg/dL (1.3 mmol/L) in women are desirable. **C** However, LDL cholesterol-targeted statin therapy remains the preferred strategy. **A**
- Combination therapy has been shown not to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended. **A**
- Statin therapy is contraindicated in pregnancy. **B**

Evidence for Benefits of Lipid-Lowering Therapy

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of CVD. Multiple clinical trials have demonstrated significant effects of pharmacological (primarily statin) therapy on CVD outcomes in subjects with CHD and for primary CVD prevention (347,348). Subanalyses of diabetic subgroups of larger trials (349–353) and trials specifically in subjects with diabetes (354,355) showed significant primary and secondary prevention of CVD events \pm CHD

deaths in diabetic patients. Meta-analyses including data from over 18,000 patients with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a 9% proportional reduction in all-cause mortality, and 13% reduction in vascular mortality, for each mmol/L reduction in LDL cholesterol (356). As in those without diabetes, absolute reductions in “hard” CVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline CVD risk (known CVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or high risk for CVD are convincing (357,358).

Diabetes With Statin Use

There is an increased risk of incident diabetes with statin use (359,360), which may be limited to those with diabetes risk factors. These patients may benefit additionally from diabetes screening when on statin therapy. In an analysis of one of the initial studies suggesting that statins are linked to risk of diabetes, the cardiovascular event rate reduction with statins outweighed the risk of incident diabetes even for patients at highest risk for diabetes (361). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin) (362). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes, while simultaneously preventing 5.4 vascular events among those 255 patients (360). The relative risk-benefit ratio favoring statins is further supported by meta-analysis of individual data of over 170,000 persons from 27 randomized trials. This demonstrated that individuals at low risk of vascular disease, including those undergoing primary prevention, received benefits from statins that included reductions in major vascular events and vascular death without increase in incidence of cancer or deaths from other causes (348).

Low levels of HDL cholesterol, often associated with elevated triglyceride

levels, are the most prevalent pattern of dyslipidemia in persons with type 2 diabetes. However, the evidence base for drugs that target these lipid fractions is significantly less robust than that for statin therapy (363). Nicotinic acid has been shown to reduce CVD outcomes (364), although the study was done in a nondiabetic cohort. Gemfibrozil has been shown to decrease rates of CVD events in subjects without diabetes (365,366) and in a subgroup with diabetes in one of the larger trials (365). However, in a large trial specific to diabetic patients, fenofibrate failed to reduce overall cardiovascular outcomes (367).

Combination Therapy

Combination therapy, with a statin and a fibrate or statin and niacin, may be efficacious for treatment for all three lipid fractions, but this combination is associated with an increased risk for abnormal transaminase levels, myositis, or rhabdomyolysis. The risk of rhabdomyolysis is higher with higher doses of statins and with renal insufficiency and seems to be lower when statins are combined with fenofibrate than gemfibrozil (368). In the ACCORD study, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke, as compared with simvastatin alone, in patients with type 2 diabetes who were at high risk for CVD. Prespecified subgroup analyses suggested heterogeneity in treatment effects according to sex, with a benefit of combination therapy for men and possible harm for women, and a possible benefit for patients with both triglyceride level ≥ 204 mg/dL and HDL cholesterol level ≤ 34 mg/dL (369). The AIM-HIGH trial randomized over 3,000 patients (about one-third with diabetes) with established CVD, low levels of HDL cholesterol, and triglyceride levels of 150–400 mg/dL to statin therapy plus extended release niacin or matching placebo. The trial was halted early due to lack of efficacy on the primary CVD outcome (first event of the composite of death from coronary heart disease (CHD), nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (370).

Hence, combination lipid-lowering therapy cannot be broadly recommended.

Dyslipidemia Treatment and Target Lipid Levels

Unless they have severe hypertriglyceridemia at risk for pancreatitis, for most diabetic patients the first priority of dyslipidemia therapy is to lower LDL cholesterol to <100 mg/dL (2.60 mmol/L) (371). Lifestyle intervention, including MNT, increased physical activity, weight loss, and smoking cessation, may allow some patients to reach lipid goals. Nutrition intervention should be tailored according to each patient's age, diabetes type, pharmacological treatment, lipid levels, and other medical conditions. Recommendations should focus on the reduction of saturated fat, cholesterol, and *trans* unsaturated fat intake and increases in n-3 fatty acids, viscous fiber (such as in oats, legumes, and citrus), and plant stanols/sterols. Glycemic control can also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control.

In those with clinical CVD or over age 40 years with other CVD risk factors, pharmacological treatment should be added to lifestyle therapy regardless of baseline lipid levels. Statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. In patients other than those described above, statin treatment should be considered if there is an inadequate LDL cholesterol response to lifestyle modifications and improved glucose control or if the patient has increased cardiovascular risk (e.g., multiple cardiovascular risk factors or long diabetes duration).

Very little clinical trial evidence exists for type 2 diabetic patients under the age of 40 years or for type 1 diabetic patients of any age. In the Heart Protection Study (lower age limit 40 years), the subgroup of ~ 600 patients with type 1 diabetes had a proportionately similar reduction in risk to patients with type 2 diabetes, although not statistically significant (350). Although the data are not definitive, similar lipid-lowering goals for both type 1 and type 2 diabetic

patients should be considered, particularly if they have other cardiovascular risk factors.

Alternative Lipoprotein Goals

Most trials of statins and CVD outcome tested specific doses of statins against placebo or other statins, rather than aiming for specific LDL cholesterol goals (372). Placebo-controlled trials generally achieved LDL cholesterol reductions of 30–40% from baseline. Hence, LDL cholesterol lowering of this magnitude is an acceptable outcome for patients who cannot reach LDL cholesterol goals due to severe baseline elevations in LDL cholesterol and/or intolerance of maximal, or any, statin doses. Additionally for those with baseline LDL cholesterol minimally above 100 mg/dL, prescribing statin therapy to lower LDL cholesterol about 30–40% from baseline is probably more effective than prescribing just enough to get LDL cholesterol slightly below 100 mg/dL.

Clinical trials in high-risk patients, such as those with acute coronary syndromes or previous cardiovascular events (373–375), have demonstrated that more aggressive therapy with high doses of statins to achieve an LDL cholesterol of <70 mg/dL led to a significant reduction in further events. A reduction in LDL cholesterol to <70 mg/dL is an option in very-high-risk diabetic patients with overt CVD (371). Some experts recommend a greater focus on non-HDL cholesterol, apolipoprotein B (apoB), or lipoprotein particle measurements to assess residual CVD risk in statin-treated patients who are likely to have small LDL particles, such as people with diabetes (376), but it is unclear whether clinical management would change with these measurements.

In individual patients, the high variable response seen with LDL cholesterol lowering with statins is poorly understood (377). Reduction of CVD events with statins correlates very closely with LDL cholesterol lowering (347). If initial attempts to prescribe a statin leads to side effects, clinicians should attempt to find a dose or alternative statin that is tolerable. There is evidence for significant LDL cholesterol lowering from even extremely low, less than daily, statin doses (378). When maximally tolerated

doses of statins fail to significantly lower LDL cholesterol (<30% reduction from the patient's baseline), there is no strong evidence that combination therapy should be used to achieve additional LDL cholesterol lowering. Niacin, fenofibrate, ezetimibe, and bile acid sequestrants all offer additional LDL cholesterol lowering to statins alone. However, there is insufficient evidence that such combination therapy for LDL cholesterol lowering provides a significant increment in CVD risk reduction over statin therapy alone.

Treatment of Other Lipoprotein Fractions or Targets

Hypertriglyceridemia should be addressed with dietary and lifestyle changes. Severe hypertriglyceridemia (>1,000 mg/dL) may warrant immediate pharmacological therapy (fibric acid derivative, niacin, or fish oil) to reduce the risk of acute pancreatitis. If severe hypertriglyceridemia is absent, then therapy targeting HDL cholesterol or triglycerides lacks the strong evidence base of statin therapy. If the HDL cholesterol is <40 mg/dL and the LDL cholesterol between 100 and 129 mg/dL, a fibrate or niacin might be used, especially if a patient is intolerant to statins. Niacin is the most effective drug for raising HDL cholesterol. It can significantly increase blood glucose at high doses, but at modest doses (750–2,000 mg/day), significant improvements in LDL cholesterol, HDL cholesterol, and triglyceride levels are accompanied by only modest changes in glucose that are generally amenable to adjustment of diabetes therapy (370,379,380).

Table 10 summarizes common treatment goals for A1C, blood pressure, and LDL cholesterol.

3. Antiplatelet Agents

Recommendations

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). **C**
- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk <5%, such as in men aged <50 years and women aged <60 years with no major additional CVD risk factors), since the potential adverse effects from bleeding likely offset the potential benefits. **C**
- In patients in these age-groups with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. **E**
- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes with a history of CVD. **A**
- For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. **B**

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with

Table 10—Summary of recommendations for glycemic, blood pressure, and lipid control for most adults with diabetes

A1C	<7.0%*
Blood pressure	<140/80 mmHg**
Lipids	
LDL cholesterol	<100 mg/dL (<2.6 mmol/L) [†] Statin therapy for those with history of MI or age over 40 plus other risk factors

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. **Based on patient characteristics and response to therapy, lower SBP targets may be appropriate. [†]In individuals with overt CVD, a lower LDL cholesterol goal of <70 mg/dL (1.8 mmol/L), using a high dose of a statin, is an option.

previous MI or stroke (secondary prevention). Its net benefit in primary prevention among patients with no previous cardiovascular events is more controversial, both for patients with and without a history of diabetes (381,382). Two RCTs of aspirin specifically in patients with diabetes failed to show a significant reduction in CVD end points, raising further questions about the efficacy of aspirin for primary prevention in people with diabetes (190,383).

The Antithrombotic Trialists' (ATT) collaborators published an individual patient-level meta-analysis of the six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of vascular events by 12% (RR 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI with little effect on CHD death (RR 0.95 [95% CI 0.78–1.15]) or total stroke. There was some evidence of a difference in aspirin effect by sex: aspirin significantly reduced CVD events in men, but not in women. Conversely, aspirin had no effect on stroke in men but significantly reduced stroke in women. Notably, sex differences in aspirin's effects have not been observed in studies of secondary prevention (381). In the six trials examined by the ATT collaborators, the effects of aspirin on major vascular events were similar for patients with or without diabetes: RR 0.88 (95% CI 0.67–1.15) and 0.87 (0.79–0.96), respectively. The confidence interval was wider for those with diabetes because of their smaller number.

Based on the currently available evidence, aspirin appears to have a modest effect on ischemic vascular events with the absolute decrease in events depending on the underlying CVD risk. The main adverse effects appear to be an increased risk of gastrointestinal bleeding. The excess risk may be as high as 1–5 per 1,000 per year in real-world settings. In adults with CVD risk greater than 1% per year, the number of CVD events prevented will be similar to or greater than the number of episodes of bleeding induced, although these complications

do not have equal effects on long-term health (384).

In 2010, a position statement of the ADA, the American Heart Association (AHA), and the American College of Cardiology Foundation (ACCF) recommends that low-dose (75–162 mg/day) aspirin for primary prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10-year risk of CVD events over 10%) and who are not at increased risk for bleeding. This generally includes most men over age 50 years and women over age 60 years who also have one or more of the following major risk factors: 1) smoking, 2) hypertension, 3) dyslipidemia, 4) family history of premature CVD, and 5) albuminuria (385).

However, aspirin is no longer recommended for those at low CVD risk (women under age 60 years and men under age 50 years with no major CVD risk factors; 10-year CVD risk under 5%) as the low benefit is likely to be outweighed by the risks of significant bleeding. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors; those with 10-year CVD risk of 5–10%) until further research is available. Aspirin use in patients under the age of 21 years is contraindicated due to the associated risk of Reye syndrome.

Average daily dosages used in most clinical trials involving patients with diabetes ranged from 50 to 650 mg but were mostly in the range of 100 to 325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dosage may help reduce side effects (386). In the U.S., the most common low dose tablet is 81 mg. Although platelets from patients with diabetes have altered function, it is unclear what, if any, impact that finding has on the required dose of aspirin for cardioprotective effects in the patient with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A₂ and thus not sensitive to the effects of aspirin (387). Therefore, while "aspirin resistance" appears higher in the diabetic patients when measured by a

variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B₂), these observations alone are insufficient to empirically recommend higher doses of aspirin be used in the diabetic patient at this time.

A P2Y₁₂ receptor antagonist in combination with aspirin should be used for at least 1 year in patients following an acute coronary syndrome. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention (PCI) was performed, and the use of clopidogrel, ticagrelor, or prasugrel if PCI was performed (388).

4. Smoking Cessation Recommendations

- Advise all patients not to smoke or use tobacco products. **A**
- Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. **B**

Results from epidemiological, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and health risks. Much of the work documenting the effect of smoking on health did not separately discuss results on subsets of individuals with diabetes, but suggests that the identified risks are at least equivalent to those found in the general population. Other studies of individuals with diabetes consistently demonstrate that smokers (and persons exposed to second-hand smoke) have a heightened risk of CVD, premature death, and increased rate of microvascular complications of diabetes. Smoking may have a role in the development of type 2 diabetes. One study in smokers with newly diagnosed type 2 diabetes found that smoking cessation was associated with amelioration of metabolic parameters and reduced blood pressure and albuminuria at 1 year (389).

The routine and thorough assessment of tobacco use is key to prevent smoking or encourage cessation. Numerous large randomized clinical trials have demonstrated the efficacy and cost-effectiveness of brief counseling in smoking cessation, including the use of quitlines, in reducing tobacco use.

For the patient motivated to quit, the addition of pharmacological therapy to counseling is more effective than either treatment alone. Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse (390). Although some patients may gain weight in the period shortly after smoking cessation, recent research has demonstrated that this weight gain does not diminish the substantial CVD risk benefit realized from smoking cessation (391).

5. Cardiovascular Disease Recommendations Screening

- In asymptomatic patients, routine screening for CAD is not recommended because it does not improve outcomes as long as CVD risk factors are treated. **A**

Treatment

- In patients with known CVD, consider ACE inhibitor therapy **C** and use aspirin and statin therapy **A** (if not contraindicated) to reduce the risk of cardiovascular events.
- In patients with a prior MI, β -blockers should be continued for at least 2 years after the event. **B**
- In patients with symptomatic heart failure, avoid thiazolidinedione treatment. **C**
- In patients with stable CHF, metformin may be used if renal function is normal but should be avoided in unstable or hospitalized patients with CHF. **B**

In all patients with diabetes, cardiovascular risk factors should be assessed at least annually. These risk factors include dyslipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of albuminuria. Abnormal risk factors should be treated as described elsewhere in these guidelines. Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Look AHEAD trial may be considered for improving glucose control, fitness, and some CVD risk factors. However, it is not

recommended to reduce CVD events in overweight or obese adults with type 2 diabetes (155). Patients at increased CVD risk should receive aspirin and a statin, and ACE inhibitor or ARB therapy if hypertensive, unless there are contraindications to a particular drug class. While clear benefit exists for ACE inhibitor and ARB therapy in patients with nephropathy or hypertension, the benefits in patients with CVD in the absence of these conditions are less clear, especially when LDL cholesterol is concomitantly controlled (392,393).

Candidates for advanced or invasive cardiac testing include those with 1) typical or atypical cardiac symptoms and 2) an abnormal resting ECG. The screening of asymptomatic patients with high CVD risk is not recommended (257), in part because these high-risk patients should already be receiving intensive medical therapy, an approach that provides similar benefit as invasive revascularization (394,395). There is also some evidence that silent MI may reverse over time, adding to the controversy concerning aggressive screening strategies (396). Finally, a recent randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (397). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, the overall effectiveness, especially the cost-effectiveness, of such an indiscriminate screening strategy is now questioned.

Despite the intuitive appeal, recent studies have found that a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up for CAD fails to identify which patients with type 2 diabetes will have silent ischemia on screening tests (398,399). The effectiveness of newer noninvasive CAD screening methods, such as computed tomography (CT) and CT angiography, to identify patient subgroups for different treatment strategies remains unproven. Although asymptomatic diabetic patients found to have a higher coronary disease

burden have more future cardiac events (400–402), the role of these tests beyond risk stratification is not clear. Their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive CVD risk factor control.

A systematic review of 34,000 patients showed that metformin is as safe as other glucose-lowering treatments in patients with diabetes and CHF, even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease (CKD); however, metformin should be avoided in hospitalized patients (403).

B. Nephropathy

General Recommendations

- Optimize glucose control to reduce the risk or slow the progression of nephropathy. **A**
- Optimize blood pressure control to reduce the risk or slow the progression of nephropathy. **A**

Screening

- Perform an annual test to quantitate urine albumin excretion in type 1 diabetic patients with diabetes duration of ≥ 5 years and in all type 2 diabetic patients starting at diagnosis. **B**

Treatment

- An ACE inhibitor or ARB for the primary prevention of diabetic kidney disease is not recommended in diabetic patients with normal blood pressure and albumin excretion < 30 mg/24 h. **B**
- Either ACE inhibitors or ARBs (but not both in combination) are recommended for the treatment of the nonpregnant patient with modestly elevated (30–299 mg/24 h) **C** or higher levels (> 300 mg/24 h) of urinary albumin excretion. **A**
- For people with diabetes and diabetic kidney disease (albuminuria > 30 mg/24 h), reducing the amount of dietary protein below usual intake is not recommended because it does not

alter glycemic measures, cardiovascular risk measures, or the course of GFR decline. **A**

- When ACE inhibitors, ARBs, or diuretics are used, monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium. **E**
- Continued monitoring of urine albumin excretion to assess both response to therapy and progression of disease is reasonable. **E**
- When eGFR is <60 mL/min/1.73 m², evaluate and manage potential complications of CKD. **E**
- Consider referral to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, or advanced kidney disease. **B**

To be consistent with newer nomenclature intended to emphasize the continuous nature of albuminuria as a risk factor, the terms “microalbuminuria” (30–299 mg/24 h) and “macroalbuminuria” (>300 mg/24 h) will no longer be used, but rather referred to as persistent albuminuria at levels 30–299 mg/24 h and levels ≥ 300 mg/24 h. Normal albumin excretion is currently defined as <30 mg/24 h.

Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of ESRD. Persistent albuminuria in the range of 30–299 mg/24 h has been shown to be an early stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes. It is a well-established marker of increased CVD risk (404–406). However, there is increasing evidence of spontaneous remission of albumin levels 30–299 mg/24 h in up to 40% of patients with type 1 diabetes. About 30–40% remain with 30–299 mg/24 h and do not progress to more elevated levels of albuminuria (≥ 300 mg/24 h) over 5–10 years of follow-up (407–410). Patients with persistent albuminuria (30–299 mg/24 h) who progress to more significant levels (≥ 300 mg/24 h) are likely to progress to ESRD (411,412).

A number of interventions have been demonstrated to reduce the risk and slow the progression of renal disease. Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of increased urinary albumin excretion in patients with type 1 (413) and type 2 (85,86,89,90) diabetes. The UKPDS provided strong evidence that blood pressure control can reduce the development of nephropathy (323). In addition, large prospective randomized studies in patients with type 1 diabetes have demonstrated that achievement of lower levels of SBP (<140 mmHg) resulting from treatment using ACE inhibitors provides a selective benefit over other antihypertensive drug classes in delaying the progression of increased urinary albumin excretion and can slow the decline in GFR in patients with higher levels of albuminuria (414,415). In type 2 diabetes with hypertension and normoalbuminuria, RAS inhibition has been demonstrated to delay onset of elevated albuminuria (416,417). In the latter study, there was an unexpected higher rate of fatal cardiovascular events with olmesartan among patients with preexisting CHD.

ACE inhibitors have been shown to reduce major CVD outcomes (i.e., MI, stroke, death) in patients with diabetes (338), thus further supporting the use of these agents in patients with elevated albuminuria, a CVD risk factor. ARBs do not prevent onset of elevated albuminuria in normotensive patients with type 1 or type 2 diabetes (418,419); however, ARBs have been shown to reduce the progression rate of albumin levels from 30 to 299 mg/24 h to levels ≥ 300 mg/24 h as well as ESRD in patients with type 2 diabetes (420–422). Some evidence suggests that ARBs have a smaller magnitude of rise in potassium compared with ACE inhibitors in people with nephropathy (423).

In the absence of side effects or adverse events (e.g., hyperkalemia or acute kidney injury), it is suggested to titrate up to the maximum approved dose for the treatment of hypertension. Combinations of drugs that block the

renin-angiotensin-aldosterone system (e.g., an ACE inhibitor plus an ARB, a mineralocorticoid antagonist, or a direct renin inhibitor) provide additional lowering of albuminuria (424–427). However, such combinations have been found to provide no additional cardiovascular benefit and have higher adverse event rates (428). At least one randomized clinical trial has shown an increase in adverse events, particularly impaired kidney function and hyperkalemia, compared with either agent alone, despite a reduction in albuminuria using combination therapy (410).

Diuretics, calcium channel blockers, and β -blockers should be used as additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs (343) or as alternate therapy in the rare individual unable to tolerate ACE inhibitors or ARBs.

Studies in patients with varying stages of nephropathy have shown that protein restriction of dietary protein helps slow the progression of albuminuria, GFR decline, and occurrence of ESRD (429–432), although more recent studies have provided conflicting results (157). Dietary protein restriction might be considered particularly in patients whose nephropathy seems to be progressing despite optimal glucose and blood pressure control and use of ACE inhibitor and/or ARBs (432).

Assessment of Albuminuria Status and Renal Function

Screening for increased urinary albumin excretion can be performed by measurement of the albumin-to-creatinine ratio in a random spot collection; 24-h or timed collections are more burdensome and add little to prediction or accuracy (433,434). Measurement of a spot urine for albumin alone (whether by immunoassay or by using a dipstick test specific for albuminuria) without simultaneously measuring urine creatinine is less expensive but susceptible to false-negative and -positive determinations as a result of variation in urine concentration due to hydration and other factors.

Abnormalities of albumin excretion and the linkage between albumin-to-creatinine

ratio and 24-h albumin excretion are defined in **Table 11**. Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have developed increased urinary albumin excretion or had a progression in albuminuria. Exercise within 24 h, infection, fever, CHF, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values.

Information on presence of abnormal urine albumin excretion in addition to level of GFR may be used to stage CKD. The National Kidney Foundation classification (**Table 12**) is primarily based on GFR levels and may be superseded by other systems in which staging includes other variables such as urinary albumin excretion (435). Studies have found decreased GFR in the absence of increased urine albumin excretion in a substantial percentage of adults with diabetes (436). Substantial evidence shows that in patients with type 1 diabetes and persistent albumin levels 30–299 mg/24 h, screening with albumin excretion rate alone would miss >20% of progressive disease (410). Serum creatinine with estimated GFR should therefore be assessed at least annually in all adults with diabetes, regardless of the degree of urine albumin excretion.

Serum creatinine should be used to estimate GFR and to stage the level of CKD, if present. eGFR is commonly coreported by laboratories or can be estimated using formulae such as the Modification of Diet in Renal Disease (MDRD) study equation (437) or the

Table 11—Definitions of abnormalities in albumin excretion

Category	Spot collection ($\mu\text{g}/\text{mg}$ creatinine)
Normal	<30
Increased urinary albumin excretion*	≥ 30

*Historically, ratios between 30 and 299 have been called microalbuminuria and those 300 or greater have been called macroalbuminuria (or clinical albuminuria).

Table 12—Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m ² body surface area)
1	Kidney damage* with normal or increased GFR	≥ 90
2	Kidney damage* with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or dialysis

*Kidney damage defined as abnormalities on pathologic, urine, blood, or imaging tests. Adapted from Levey et al. (434).

CKD-EPI equation. GFR calculators are available at <http://www.nkdep.nih.gov>.

The role of continued annual quantitative assessment of albumin excretion after diagnosis of albuminuria and institution of ACE inhibitor or ARB therapy and blood pressure control is unclear. Continued surveillance can assess both response to therapy and progression of disease. Some suggest that reducing albuminuria to the normal (<30 mg/g) or near-normal range may improve renal and cardiovascular prognosis, but this approach has not been formally evaluated in prospective trials, and more recent evidence reported spontaneous remission of albuminuria in up to 40% of type 1 diabetic patients.

Conversely, patients with increasing albumin levels, declining GFR, increasing blood pressure, retinopathy, macrovascular disease, elevated lipids and/or uric acid concentrations, or a family history of CKD are more likely to experience a progression of diabetic kidney disease (410).

Complications of kidney disease correlate with level of kidney function. When the eGFR is <60 mL/min/1.73 m², screening for complications of CKD is indicated (**Table 13**). Early vaccination against HBV is indicated in patients likely to progress to end-stage kidney disease.

Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in GFR, and resistant hypertension). Other triggers for referral may include difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, or electrolyte disturbance) or

advanced kidney disease. The threshold for referral may vary depending on the frequency with which a provider encounters diabetic patients with significant kidney disease. Consultation with a nephrologist when stage 4 CKD develops has been found to reduce cost, improve quality of care, and keep people off dialysis longer (438). However, nonrenal specialists should not delay educating their patients about the progressive nature of diabetic kidney disease, the renal preservation benefits of aggressive treatment of blood pressure, blood glucose, and hyperlipidemia, and the potential need for renal transplant.

C. Retinopathy

General Recommendations

- Optimize glycemic control to reduce the risk or slow the progression of retinopathy. **A**
- Optimize blood pressure control to reduce the risk or slow the progression of retinopathy. **A**

Screening

- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes. **B**
- If there is no evidence of retinopathy for one or more eye exams, then exams every 2 years may be considered. If diabetic retinopathy is present, subsequent examinations for type 1 and type 2 diabetic patients

Table 13—Management of CKD in diabetes

GFR	Recommended
All patients	Yearly measurement of creatinine, urinary albumin excretion, potassium
45–60	Referral to a nephrologist if possibility for nondiabetic kidney disease exists (duration of type 1 diabetes <10 years, heavy proteinuria, abnormal findings on renal ultrasound, resistant hypertension, rapid fall in GFR, or active urinary sediment on ultrasound) Consider need for dose adjustment of medications Monitor eGFR every 6 months Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, parathyroid hormone at least yearly Assure vitamin D sufficiency Consider bone density testing Referral for dietary counseling
30–44	Monitor eGFR every 3 months Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, weight every 3–6 months Consider need for dose adjustment of medications
<30	Referral to a nephrologist

Adapted from http://www.kidney.org/professionals/KDOQI/guideline_diabetes.

should be repeated annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight threatening, then examinations will be required more frequently. **B**

- High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. **E**
- Women with preexisting diabetes who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examination should occur in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum. **B**

Treatment

- Promptly refer patients with any level of macular edema, severe NPDR, or any PDR to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. **A**
- Laser photocoagulation therapy is indicated to reduce the risk of vision

loss in patients with high-risk PDR, clinically significant macular edema, and in some cases severe NPDR. **A**

- Anti-vascular endothelial growth factor (VEGF) therapy is indicated for diabetic macular edema. **A**
- The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as this therapy does not increase the risk of retinal hemorrhage. **A**

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to the duration of diabetes. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to duration of diabetes, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (439), nephropathy (440), and hypertension (441). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy (76,85,86,442). Lowering blood pressure has been shown to decrease the progression of retinopathy (323),

although tight targets (systolic <120 mmHg) do not impart additional benefit (442). Several case series and a controlled prospective study suggest that pregnancy in type 1 diabetic patients may aggravate retinopathy (443,444). Laser photocoagulation surgery can minimize this risk (444).

One of the main motivations for screening for diabetic retinopathy is the long-established efficacy of laser photocoagulation surgery in preventing visual loss. Two large trials, the Diabetic Retinopathy Study (DRS) in patients with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in patients with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (445) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes, with greatest risk-benefit ratio in those with baseline disease (disc neovascularization or vitreous hemorrhage).

The ETDRS (446) established the benefit of focal laser photocoagulation surgery in eyes with macular edema, particularly those with clinically significant macular edema, with reduction of doubling of the visual angle (e.g., 20/50 to 20/100) from 20% in untreated eyes to 8% in treated eyes. The ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset patients with severe NPDR or less-than-high-risk PDR.

Laser photocoagulation surgery in both trials was beneficial in reducing the risk of further visual loss, but generally not beneficial in reversing already diminished acuity. Recombinant monoclonal neutralizing antibody to VEGF improves vision and reduces the need for laser photocoagulation in patients with macular edema (447). Other emerging therapies for retinopathy include sustained intravitreal delivery of fluocinolone (448) and the possibility of prevention with fenofibrate (449,450).

The preventive effects of therapy and the fact that patients with PDR or macular edema may be asymptomatic

provide strong support for a screening program to detect diabetic retinopathy. Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diabetes (451). Patients with type 2 diabetes, who may have had years of undiagnosed diabetes and who have a significant risk of prevalent diabetic retinopathy at time of diagnosis should have an initial dilated and comprehensive eye examination. Examinations should be performed by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing diabetic retinopathy. Subsequent examinations for type 1 and type 2 diabetic patients are generally repeated annually. Exams every 2 years may be cost-effective after one or more normal eye exams, and in a population with well-controlled type 2 diabetes there was essentially no risk of development of significant retinopathy with a 3-year interval after a normal examination (452). Examinations will be required more frequently if retinopathy is progressing.

Retinal photography, with remote reading by experts, has great potential in areas where qualified eye care professionals are not available. It may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (453). In-person exams are still necessary when the photos are unacceptable and for follow-up of abnormalities detected. Photos are not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Results of eye examinations should be documented and transmitted to the referring health care professional.

D. Neuropathy Recommendations

- All patients should be screened for distal symmetric polyneuropathy (DPN) starting at diagnosis of type 2 diabetes and 5 years after the

diagnosis of type 1 diabetes and at least annually thereafter, using simple clinical tests. **B**

- Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical. **E**
- Screening for signs and symptoms of CAN should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Special testing is rarely needed and may not affect management or outcomes. **E**
- Medications for the relief of specific symptoms related to painful DPN and autonomic neuropathy are recommended because they may reduce pain **B** and improve quality of life. **E**

The diabetic neuropathies are heterogeneous with diverse clinical manifestations. They may be focal or diffuse. The most prevalent neuropathies are chronic sensorimotor DPN and autonomic neuropathy. Although DPN is a diagnosis of exclusion, complex investigations or referral for neurology consultation to exclude other conditions is rarely needed.

The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons:

1. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.
2. A number of treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of DPN may be asymptomatic and patients are at risk for insensate injury to their feet.
4. Autonomic neuropathy and particularly CAN is an independent risk factor for cardiovascular mortality (261,454).

Specific treatment for the underlying nerve damage is currently not available, other than improved glycemic control, which may modestly slow progression in type 2 diabetes (90) but not reverse neuronal loss.

Effective symptomatic treatments are available for the neuropathic pain of DPN such as neuropathic pain (455) and for limited symptoms of autonomic neuropathy.

Diagnosis of Neuropathy

Distal Symmetric Polyneuropathy. Patients with diabetes should be screened annually for DPN symptoms using simple clinical tests. Symptoms vary according to the class of sensory fibers involved. The most common symptoms are induced by the involvement of small fibers and include pain, dysesthesias (unpleasant abnormal sensations of burning and tingling associated with peripheral nerve lesions), and numbness. Clinical tests include assessment of vibration threshold using a 128-Hz tuning fork, pinprick sensation and light touch perception using a 10-g monofilament, and ankle reflexes. Assessment should follow the typical DPN pattern, starting distally (the dorsal aspect of the hallux) on both sides and move proximally until threshold is detected. Several clinical instruments that combine more than one test have >87% sensitivity in detecting DPN (83,456,457).

In patients with severe or atypical neuropathy, causes other than diabetes should always be considered, such as neurotoxic medications, heavy metal poisoning, alcohol abuse, vitamin B₁₂ deficiency (especially in those taking metformin for prolonged periods) (458), renal disease, chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (459).

Diabetic Autonomic Neuropathy. The symptoms and signs of autonomic dysfunction should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, and, potentially, autonomic failure in response to hypoglycemia.

Cardiovascular Autonomic Neuropathy. CAN is the most studied and clinically important form of diabetic autonomic

neuropathy because of its association with mortality risk independent of other cardiovascular risk factors (261,397). In early stages CAN may be completely asymptomatic and detected by changes in heart rate variability and abnormal cardiovascular reflex tests (R-R response to deep breathing, standing and Valsalva maneuver). Advanced disease may be indicated by resting tachycardia (>100 bpm) and orthostasis (a fall in SBP >20 mmHg or DBP of at least 10 mmHg upon standing without an appropriate heart rate response). The standard cardiovascular reflex testing, especially the deep-breathing test, is noninvasive, easy to perform, reliable, and reproducible and has prognostic value. Although some societies have developed guidelines for screening for CAN, the benefits of sophisticated testing beyond risk stratification are not clear (460).

Gastrointestinal Neuropathies.

Gastrointestinal neuropathies (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, fecal incontinence) may involve any section of the gastrointestinal tract. Gastroparesis should be suspected in individuals with erratic glucose control or with upper gastrointestinal symptoms without other identified cause. Evaluation of solid-phase gastric emptying using double-isotope scintigraphy may be done if symptoms are suggestive, but test results often correlate poorly with symptoms. Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea.

Genitourinary Tract Disturbances.

Diabetic autonomic neuropathy is also associated with genitourinary tract disturbances. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation. Evaluation of bladder dysfunction should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Glycemic Control. Tight and stable glycemic control, implemented as early as possible has been shown to effectively prevent the development of DPN and autonomic neuropathy in

patients with type 1 diabetes for many years (461–464). While the evidence is not as strong for type 2 diabetes as for type 1 diabetes, some studies have demonstrated a modest slowing of progression (90,465) without reversal of neuronal loss. Several observational studies further suggest that neuropathic symptoms improve not only with optimization of control but also with the avoidance of extreme blood glucose fluctuations.

Distal Symmetric Polyneuropathy. DPN symptoms, and especially neuropathic pain, can be severe, have sudden onset, and are associated with lower quality of life, limited mobility, depression, and social dysfunction (466). There is limited clinical evidence regarding the most effective treatments for individual patient needs given the wide range of available medications (467,468). Two drugs have been approved for relief of DPN pain in the U.S.—pregabalin and duloxetine—but neither of these affords complete relief, even when used in combination. Venlafaxine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release) may also be effective and could be considered for treatment of painful DPN. Head-to-head treatment comparisons and studies that include quality-of-life outcomes are rare, so treatment decisions must often follow a trial-and-error approach. Given the range of partially effective treatment options, a tailored and step-wise pharmacological strategy with careful attention to relative symptom improvement, medication adherence, and medication side effects is recommended to achieve pain reduction and improve quality of life (455).

Autonomic Neuropathy. An intensive multifactorial cardiovascular risk intervention targeting glucose, blood pressure, lipids, smoking, and other lifestyle factors has been shown to reduce the progression and development of CAN among patients with type 2 diabetes (469).

Orthostatic Hypotension. Treatment of orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients

require the use of both pharmacological and nonpharmacological measures (e.g., avoiding medications that aggravate hypotension, using compressive garments over the legs and abdomen).

Gastroparesis Symptoms. Gastroparesis symptoms may improve with dietary changes and prokinetic agents such as erythromycin. Recently, the European Medicines Agency (www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/07/WC500146614.pdf) decided that risks of extrapyramidal symptoms with metoclopramide outweigh benefits. In Europe, metoclopramide use is now restricted to a maximum use of 5 days and is no longer indicated for the long-term treatment of gastroparesis. Although the FDA decision is pending, it is suggested that metoclopramide be reserved to only the most severe cases that are unresponsive to other therapies. Side effects should be closely monitored.

Erectile Dysfunction. Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. Interventions for other manifestations of autonomic neuropathy are described in the ADA statement on neuropathy (468). As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process, but may have a positive impact on the quality of life of the patient.

E. Foot Care

Recommendations

- For all patients with diabetes, perform an annual comprehensive foot examination to identify risk factors predictive of ulcers and amputations. The foot examination should include inspection, assessment of foot pulses, and testing for loss of protective sensation (LOPS) (10-g monofilament plus testing any one of the following: vibration using 128-Hz tuning fork, pinprick sensation, ankle reflexes, or vibration perception threshold). **B**
- Provide general foot self-care education to all patients with diabetes. **B**

- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet, especially those with a history of prior ulcer or amputation. **B**
- Refer patients who smoke, have LOPS and structural abnormalities, or have history of prior lower-extremity complications to foot care specialists for ongoing preventive care and lifelong surveillance. **C**
- Initial screening for peripheral arterial disease (PAD) should include a history for claudication and an assessment of the pedal pulses. Consider obtaining an ankle-brachial index (ABI), as many patients with PAD are asymptomatic. **C**
- Refer patients with significant claudication or a positive ABI for further vascular assessment and consider exercise, medications, and surgical options. **C**

Amputation and foot ulceration, consequences of diabetic neuropathy and/or PAD, are common and are major causes of morbidity and disability in people with diabetes. Loss of 10-g monofilament perception and reduced vibration perception predict foot ulcers (468). Early recognition and management of risk factors can prevent or delay adverse outcomes.

The risk of ulcers or amputations is increased in people who have the following risk factors:

- Previous amputation
- Past foot ulcer history
- Peripheral neuropathy
- Foot deformity
- Peripheral vascular disease
- Visual impairment
- Diabetic nephropathy (especially patients on dialysis)
- Poor glycemic control
- Cigarette smoking

In 2008, ADA published screening recommendations (470). Clinicians are encouraged to review this report for further details and practical descriptions of how to perform components of the comprehensive foot examination.

Examination

All adults with diabetes should undergo a comprehensive foot

examination to identify high-risk conditions at least annually. Clinicians should ask about history of previous foot ulceration or amputation, neuropathic or peripheral vascular symptoms, impaired vision, tobacco use, and foot care practices. A general inspection of skin integrity and musculoskeletal deformities should be done in a well-lit room. Vascular assessment would include inspection and assessment of pedal pulses.

The neurological exam recommended is designed to identify LOPS rather than early neuropathy. The clinical examination to identify LOPS is simple and requires no expensive equipment. Five simple clinical tests (use of a 10-g monofilament, vibration testing using a 128-Hz tuning fork, tests of pinprick sensation, ankle reflex assessment, and testing vibration perception threshold with a biothesiometer), each with evidence from well-conducted prospective clinical cohort studies, are considered useful in the diagnosis of LOPS in the diabetic foot. The task force agreed that any of the five tests listed could be used by clinicians to identify LOPS, although ideally two of these should be regularly performed during the screening exam—normally the 10-g monofilament and one other test. One or more abnormal tests would suggest LOPS, while at least two normal tests (and no abnormal test) would rule out LOPS. The last test listed, vibration assessment using a biothesiometer or similar instrument, is widely used in the U.S.; however, identification of the patient with LOPS can easily be carried out without this or other expensive equipment.

Screening

Initial screening for PAD should include a history for claudication and an assessment of the pedal pulses. A diagnostic ABI should be performed in any patient with symptoms of PAD. Due to the high estimated prevalence of PAD in patients with diabetes and the fact that many patients with PAD are asymptomatic, an ADA consensus statement on PAD (471) suggested that a screening ABI be performed in patients over 50 years of age and be considered in patients under 50 years of age who have other PAD risk factors

(e.g., smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years). Refer patients with significant symptoms or a positive ABI for further vascular assessment and consider exercise, medications, and surgical options (471).

Patient Education

Patients with diabetes and high-risk foot conditions should be educated regarding their risk factors and appropriate management. Patients at risk should understand the implications of LOPS, the importance of foot monitoring on a daily basis, the proper care of the foot, including nail and skin care, and the selection of appropriate footwear. Patients with LOPS should be educated on ways to substitute other sensory modalities (hand palpation, visual inspection) for surveillance of early foot problems. Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist in their care.

Treatment

People with neuropathy or evidence of increased plantar pressure (e.g., erythema, warmth, callus, or measured pressure) may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure. Callus can be debrided with a scalpel by a foot care specialist or other health professional with experience and training in foot care. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extra-wide or -deep shoes. People with extreme bony deformities (e.g., Charcot foot) who cannot be accommodated with commercial therapeutic footwear may need custom-molded shoes.

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci (GPC), and especially staphylococci, the most common causative organisms.

Wounds without evidence of soft tissue or bone infection do not require antibiotic therapy.

Empiric antibiotic therapy can be narrowly targeted at GPC in many acutely infected patients, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections require broader spectrum regimens and should be referred to specialized care centers (472). Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes. Guidelines for treatment of diabetic foot ulcers have recently been updated (472).

VII. ASSESSMENT OF COMMON COMORBID CONDITIONS

Recommendation

- Consider assessing for and addressing common comorbid conditions that may complicate the management of diabetes. **B**

Improved disease prevention and treatment efficacy means that patients with diabetes are living longer, often with multiple comorbidities requiring complicated medical regimens (473). In addition to the commonly appreciated comorbidities of obesity, hypertension, and dyslipidemia, diabetes management is often complicated by concurrent conditions such as heart failure, depression and anxiety, arthritis, and other diseases or conditions at rates higher than those of age-matched people without diabetes. These concurrent conditions present clinical challenges related to polypharmacy, prevalent symptoms, and complexity of care (474–477).

Depression

As discussed in Section V.H, depression, anxiety, and other mental health symptoms are highly prevalent in people with diabetes and are associated with worse outcomes.

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for CVD, are significantly higher (4- to 10-fold) with obesity, especially with central obesity,

in men and women (478). The prevalence in general populations with type 2 diabetes may be up to 23% (479) and in obese participants enrolled in the Look AHEAD trial exceeded 80% (480). Treatment of sleep apnea significantly improves quality of life and blood pressure control. The evidence for a treatment effect on glycemic control is mixed (481).

Fatty Liver Disease

Unexplained elevations of hepatic transaminase concentrations are significantly associated with higher BMI, waist circumference, triglycerides, and fasting insulin, and with lower HDL cholesterol. In a prospective analysis, diabetes was significantly associated with incident nonalcoholic chronic liver disease and with hepatocellular carcinoma (482). Interventions that improve metabolic abnormalities in patients with diabetes (weight loss, glycemic control, treatment with specific drugs for hyperglycemia or dyslipidemia) are also beneficial for fatty liver disease (483).

Cancer

Diabetes (possibly only type 2 diabetes) is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (484). The association may result from shared risk factors between type 2 diabetes and cancer (obesity, age, physical inactivity) but may also be due to hyperinsulinemia or hyperglycemia (485,486). Patients with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings and to reduce their modifiable cancer risk factors (obesity, smoking, physical inactivity).

Fractures

Age-matched hip fracture risk is significantly increased in both type 1 (summary RR 6.3) and type 2 diabetes (summary RR 1.7) in both sexes (487). Type 1 diabetes is associated with osteoporosis, but in type 2 diabetes an increased risk of hip fracture is seen despite higher bone mineral density (BMD) (488). In three large observational studies of older adults, femoral neck BMD T score and the WHO Fracture Risk Algorithm (FRAX) score were associated with hip and nonspine

fracture, although fracture risk was higher in diabetic participants compared with participants without diabetes for a given T score and age or for a given FRAX score risk (489). It is appropriate to assess fracture history and risk factors in older patients with diabetes and recommend BMD testing if appropriate for the patient's age and sex. Prevention strategies are the same as for the general population. For type 2 diabetic patients with fracture risk factors, avoiding use of thiazolidinediones is warranted.

Cognitive Impairment

Diabetes is associated with significantly increased risk and rate of cognitive decline and increased risk of dementia (490,491). In a 15-year prospective study of community-dwelling people over the age of 60 years, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer disease, and vascular dementia compared with rates in those with normal glucose tolerance (492). In a substudy of the ACCORD study, there were no differences in cognitive outcomes between intensive and standard glycemic control, although there was significantly less of a decrement in total brain volume by MRI in participants in the intensive arm (493). The effects of hyperglycemia and insulin on the brain are areas of intense research interest.

Low Testosterone in Men

Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder (494). Treatment in asymptomatic men is controversial. The evidence for effects of testosterone replacement on outcomes is mixed, and recent guidelines suggest that screening and treatment of men without symptoms are not recommended (495).

Periodontal Disease

Periodontal disease is more severe, but not necessarily more prevalent, in patients with diabetes than in those without (496). Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits is currently lacking (477).

Hearing Impairment

Hearing impairment, both high frequency and low/mid frequency, is more common in people with diabetes, perhaps due to neuropathy and/or vascular disease. In NHANES analysis, hearing impairment was about twice as great in people with diabetes compared with those without, after adjusting for age and other risk factors for hearing impairment (497).

VIII. DIABETES CARE IN SPECIFIC POPULATIONS

A. Children and Adolescents

1. Type 1 Diabetes

Three-quarters of all cases of type 1 diabetes are diagnosed in individuals <18 years of age. The provider must consider the unique aspects of care and management of children and adolescents with type 1 diabetes, such as changes in insulin sensitivity related to sexual maturity and physical growth, ability to provide self-care, supervision in child care and school, and unique neurological vulnerability to hypoglycemia and DKA. Attention to family dynamics, developmental stages, and physiological differences related to sexual maturity are all essential in developing and implementing an optimal diabetes regimen. Due to the paucity of clinical research in children, the recommendations for children and adolescents are less likely to be based on clinical trial evidence. However, expert opinion and a review of available and relevant experimental data are summarized in the ADA statement on care of children and adolescents with type 1 diabetes (498).

The care of a child or adolescent with type 1 diabetes should be provided by a multidisciplinary team of specialists trained in pediatric diabetes management. At the very least, education of the child and family should be provided by health care providers trained and experienced in childhood diabetes and sensitive to the challenges posed by diabetes in this age-group. It is essential that DSME, MNT, and psychosocial support be provided at diagnosis and regularly thereafter by individuals experienced with the educational, nutritional, behavioral, and emotional needs of the growing child

and family. The balance between adult supervision and self-care should be defined at the first interaction and re-evaluated at each clinic visit. This relationship will evolve as the child reaches physical, psychological, and emotional maturity.

a. Glycemic Control

Recommendation

- Consider age when setting glycemic goals in children and adolescents with type 1 diabetes. **E**

Current standards for diabetes management reflect the need to lower glucose as safely possible. This should be done with step-wise goals. Special consideration should be given to the unique risks of hypoglycemia in young children. For young children (<7 years old), glycemic goals may need to be modified since most at that age have a form of “hypoglycemic unawareness,” including immaturity of and a relative inability to recognize and respond to hypoglycemic symptoms. This places them at greater risk for severe hypoglycemia. While it was previously thought that young children were at risk for cognitive impairment after episodes of severe hypoglycemia, current data have not confirmed this (295,499,500). Furthermore, new therapeutic modalities, such as rapid and long-acting insulin analogs, technological advances (e.g., low glucose suspend), and education may mitigate the incidence of severe hypoglycemia (501). In adolescents, the DCCT demonstrated that near-normalization of blood glucose levels was more difficult to achieve compared with adults. Nevertheless, the increased frequency of basal-bolus regimens and insulin pumps in youth from infancy through adolescence has been associated with more children reaching ADA blood glucose targets (502–504) in those families in which both parents and the child with diabetes participate jointly to perform the required diabetes-related tasks. Furthermore, studies documenting neurocognitive imaging differences of hyperglycemia in children provide another compelling motivation for achieving glycemic targets (505).

In selecting glycemic goals, the long-term health benefits of achieving a

lower A1C should be balanced against the risks of hypoglycemia and the developmental burdens of intensive regimens in children and youth. Age-specific glycemic and A1C goals are presented in **Table 14**.

b. Screening and Management of Complications

i. Nephropathy

Recommendations

Screening

- Annual screening for albumin levels, with a random spot urine sample for albumin-to-creatinine ratio (ACR), should be considered for the child at the start of puberty or at age ≥ 10 years, whichever is earlier, once the youth has had diabetes for 5 years. **B**

Treatment

- Treatment with an ACE inhibitor, titrated to normalization of albumin excretion, should be considered when elevated ACR is subsequently confirmed on two additional specimens from different days. This should be obtained over a 6-month interval following efforts to improve glycemic control and normalize blood pressure for age. **E**

Recent research demonstrates the importance of good glycemic and blood pressure control, especially as diabetes duration increases (506).

ii. Hypertension

Recommendations

Screening

- Blood pressure should be measured at each routine visit. Children found to have high-normal blood pressure or hypertension should have blood pressure confirmed on a separate day. **B**

Treatment

- Initial treatment of high-normal blood pressure (SBP or DBP consistently above the 90th percentile for age, sex, and height) includes dietary intervention and exercise, aimed at weight control and increased physical activity, if appropriate. If target blood pressure is not reached with 3–6 months of lifestyle intervention, pharmacological treatment should be considered. **E**

Table 14—Plasma blood glucose and A1C goals for type 1 diabetes by age-group

Values by age (years)	Plasma blood glucose goal range (mg/dL)		A1C	Rationale
	Before meals	Bedtime/overnight		
Toddlers and preschoolers (0–6)	100–180	110–200	<8.5%	<ul style="list-style-type: none"> • Vulnerability to hypoglycemia • Insulin sensitivity • Unpredictability in dietary intake and physical activity • A lower goal (<8.0%) is reasonable if it can be achieved without excessive hypoglycemia
School age (6–12)	90–180	100–180	<8%	<ul style="list-style-type: none"> • Vulnerability of hypoglycemia • A lower goal (<7.5%) is reasonable if it can be achieved without excessive hypoglycemia
Adolescents and young adults (13–19)	90–130	90–150	<7.5%	<ul style="list-style-type: none"> • A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycemia
Key concepts in setting glycemic goals:				
<ul style="list-style-type: none"> • Goals should be individualized and lower goals may be reasonable based on benefit-risk assessment. • Blood glucose goals should be modified in children with frequent hypoglycemia or hypoglycemia unawareness. • Postprandial blood glucose values should be measured when there is a discrepancy between preprandial blood glucose values and A1C levels and to help assess glycemia in those on basal-bolus regimens. 				

- Pharmacological treatment of hypertension (SBP or DBP consistently above the 95th percentile for age, sex, and height or consistently >130/80 mmHg, if 95% exceeds that value) should be considered as soon as the diagnosis is confirmed. **E**
- ACE inhibitors should be considered for the initial pharmacological treatment of hypertension, following appropriate reproductive counseling due to its potential teratogenic effects. **E**
- The goal of treatment is blood pressure consistently <130/80 or below the 90th percentile for age, sex, and height, whichever is lower. **E**

Blood pressure measurements should be determined correctly, using the appropriate size cuff, and with the child seated and relaxed. Hypertension should be confirmed on at least three separate days. Normal blood pressure levels for age, sex, and height and appropriate methods for determinations are available online at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

iii. Dyslipidemia

Recommendations

Screening

- If there is a family history of hypercholesterolemia or a

cardiovascular event before age 55 years, or if family history is unknown, then consider obtaining a fasting lipid profile in children >2 years of age soon after the diagnosis (after glucose control has been established). If family history is not of concern, then consider the first lipid screening at puberty (≥ 10 years). For children diagnosed with diabetes at or after puberty, consider obtaining a fasting lipid profile soon after the diagnosis (after glucose control has been established). **E**

- For both age-groups, if lipids are abnormal, annual monitoring is reasonable. If LDL cholesterol values are within the accepted risk levels (<100 mg/dL [2.6 mmol/L]), a lipid profile repeated every 5 years is reasonable. **E**

Treatment

- Initial therapy may consist of optimization of glucose control and MNT using a Step 2 AHA diet aimed at a decrease in the amount of saturated fat in the diet. **E**
- After the age of 10 years, the addition of a statin in patients who, after MNT and lifestyle changes, have LDL cholesterol >160 mg/dL (4.1 mmol/L) or LDL cholesterol >130 mg/dL (3.4 mmol/L) and one or more CVD risk factors is reasonable. **E**
- The goal of therapy is an LDL cholesterol value <100 mg/dL (2.6 mmol/L). **E**

Children diagnosed with type 1 diabetes have a high risk of early subclinical (507,508) and clinical (509) CVD.

Although intervention data are lacking, the AHA categorizes children with type 1 diabetes in the highest tier for cardiovascular risk and recommends both lifestyle and pharmacological treatment for those with elevated LDL cholesterol levels (510,511). Initial therapy should be with a Step 2 AHA diet, which restricts saturated fat to 7% of total calories and restricts dietary cholesterol to 200 mg/day. Data from randomized clinical trials in children as young as 7 months of age indicate that this diet is safe and does not interfere with normal growth and development (512,513). Abnormal results from a random lipid panel should be confirmed with a fasting lipid panel. Evidence has shown that improved glucose control correlates with a more favorable lipid profile. However, improved glycemic control alone will not reverse significant dyslipidemia (514). Neither long-term safety nor cardiovascular outcome efficacy of statin therapy has been established for children. However, studies have shown short-term safety equivalent to that seen in adults and efficacy in lowering LDL cholesterol levels, improving endothelial function and causing regression of carotid intimal thickening (515–517). Statins are not approved for use under the age of 10 years, and statin treatment

should generally not be used in children with type 1 diabetes prior to this age. For postpubertal girls, issues of pregnancy prevention are paramount, since statins are category X in pregnancy (see Section VIII.B for more information).

iv. Retinopathy

Recommendations

- An initial dilated and comprehensive eye examination should be considered for the child at the start of puberty or at age ≥ 10 years, whichever is earlier, once the youth has had diabetes for 3–5 years. **B**
- After the initial examination, annual routine follow-up is generally recommended. Less frequent examinations may be acceptable on the advice of an eye care professional. **E**

Although retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (518), it has been reported in prepubertal children and with diabetes duration of only 1–2 years. Referrals should be made to eye care professionals with expertise in diabetic retinopathy, an understanding of retinopathy risk in the pediatric population, and experience in counseling the pediatric patient and family on the importance of early prevention/intervention.

v. Celiac Disease

Recommendations

- Consider screening children with type 1 diabetes for celiac disease by measuring IgA antitissue transglutaminase or antiendomysial antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes. **E**
- Testing should be considered in children with a positive family history of celiac disease, growth failure, failure to gain weight, weight loss, diarrhea, flatulence, abdominal pain, or signs of malabsorption or in children with frequent unexplained hypoglycemia or deterioration in glycemic control. **E**
- Consider referral to a gastroenterologist for evaluation with possible endoscopy and biopsy for confirmation of celiac

disease in asymptomatic children with positive antibodies. **E**

- Children with biopsy-confirmed celiac disease should be placed on a gluten-free diet and have consultation with a dietitian experienced in managing both diabetes and celiac disease. **B**

Celiac disease is an immune-mediated disorder that occurs with increased frequency in patients with type 1 diabetes (1–16% of individuals compared with 0.3–1% in the general population) (519,520). Symptoms of celiac disease include diarrhea, weight loss or poor weight gain, growth failure, abdominal pain, chronic fatigue, malnutrition due to malabsorption, and other gastrointestinal problems, and unexplained hypoglycemia or erratic blood glucose concentrations.

Screening

Screening for celiac disease includes measuring serum levels of tissue transglutaminase or antiendomysial antibodies, then small-bowel biopsy in antibody-positive children. European guidelines on screening for celiac disease in children (not specific to children with type 1 diabetes) suggested that biopsy may not be necessary in symptomatic children with positive antibodies, as long as further testing such as genetic or HLA testing was supportive, but that asymptomatic at-risk children should have biopsies (521). One small study that included children with and without type 1 diabetes suggested that antibody-positive but biopsy-negative children were similar clinically to those who were biopsy-positive.

Treatment

Biopsy-negative children had benefits from a gluten-free diet, but worsening on a usual diet (522). This was a small study, and children with type 1 diabetes already follow a careful diet. However, it is difficult to advocate for not confirming the diagnosis by biopsy before recommending a lifelong gluten-free diet, especially in asymptomatic children. In symptomatic children with type 1 diabetes and celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (523).

vi. Hypothyroidism

Recommendations

- Consider screening children with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after diagnosis. **E**
- Measuring thyroid-stimulating hormone (TSH) concentrations soon after diagnosis of type 1 diabetes, after metabolic control has been established, is reasonable. If normal, consider rechecking every 1–2 years, especially if the patient develops symptoms of thyroid dysfunction, thyromegaly, an abnormal growth rate, or unusual glycemic variation. **E**

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with type 1 diabetes (524). About one-quarter of type 1 diabetic children have thyroid autoantibodies at the time of diagnosis (525), and the presence of thyroid autoantibodies is predictive of thyroid dysfunction, generally hypothyroidism but less commonly hyperthyroidism (526). Subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia (527) and with reduced linear growth (528). Hyperthyroidism alters glucose metabolism, potentially resulting in deterioration of metabolic control.

c. Self-Management

No matter how sound the medical regimen, it can only be as good as the ability of the family and/or individual to implement it. Family involvement remains an important component of optimal diabetes management throughout childhood and adolescence. Health care providers who care for children and adolescents, therefore, must be capable of evaluating the educational, behavioral, emotional, and psychosocial factors that impact implementation of a treatment plan and must work with the individual and family to overcome barriers or redefine goals as appropriate.

d. School and Day Care

Since a large portion of a child's day is spent in school, close communication with and cooperation of school or day care personnel is essential for optimal

diabetes management, safety, and maximal academic opportunities. See the ADA position statement “Diabetes Care in the School and Day Care Setting” (529) for further discussion.

e. Transition From Pediatric to Adult Care

Recommendations

- As teens transition into emerging adulthood, health care providers and families must recognize their many vulnerabilities **B** and prepare the developing teen, beginning in early to mid adolescence and at least 1 year prior to the transition. **E**
- Both pediatricians and adult health care providers should assist in providing support and links to resources for the teen and emerging adult. **B**

Care and close supervision of diabetes management is increasingly shifted from parents and other older adults throughout childhood and adolescence; however, the shift from pediatrics to adult health care providers often occurs very abruptly as the older teen enters the next developmental stage referred to as emerging adulthood (530), a critical period for young people who have diabetes. During this period of major life transitions, youth begin to move out of their parents’ home and must become more fully responsible for their diabetes care including the many aspects of self-management, making medical appointments, and financing health care once they are no longer covered under their parents health insurance (531,532). In addition to lapses in health care, this is also a period of deterioration in glycemic control, increased occurrence of acute complications, psycho-social-emotional-behavioral issues, and emergence of chronic complications (531–534).

Though scientific evidence continues to be limited, it is clear that early and ongoing attention be given to comprehensive and coordinated planning for seamless transition of all youth from pediatric to adult health care (531,532). A comprehensive discussion regarding the challenges faced during this period, including

specific recommendations, is found in the ADA position statement “Diabetes Care for Emerging Adults: Recommendations for Transition From Pediatric to Adult Diabetes Care Systems” (532).

The National Diabetes Education Program (NDEP) has materials available to facilitate the transition process (<http://ndep.nih.gov/transitions/>), and The Endocrine Society in collaboration with ADA and other organizations has developed transition tools for clinicians and youth/families (http://www.endo-society.org/clinicalpractice/transition_of_care.cfm).

2. Type 2 Diabetes

The CDC recently published projections for type 2 diabetes prevalence using the SEARCH database. Assuming a 2.3% annual increase, the prevalence of type 2 diabetes in those under 20 years of age will quadruple in 40 years (31,38). Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. Autoantigens and ketosis may be present in a substantial number of patients with features of type 2 diabetes (including obesity and acanthosis nigricans). Such a distinction at diagnosis is critical since treatment regimens, educational approaches, dietary counsel, and outcomes will differ markedly between the two diagnoses.

Type 2 diabetes has a significant incidence of comorbidities already present at the time of diagnosis (535). It is recommended that blood pressure measurement, a fasting lipid profile, assessment for albumin excretion, and dilated eye examination be performed at diagnosis. Thereafter, screening guidelines and treatment recommendations for hypertension, dyslipidemia, albumin excretion, and retinopathy in youth with type 2 diabetes are similar to those for youth with type 1 diabetes. Additional problems that may need to be addressed include polycystic ovarian disease and the various comorbidities associated with pediatric obesity such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns. The ADA consensus statement on this subject

(32) provides guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in young people.

3. Monogenic Diabetes Syndromes

Monogenic forms of diabetes (neonatal diabetes or maturity-onset diabetes of the young) represent a small fraction of children with diabetes (<5%), but readily available commercial genetic testing now enables a true genetic diagnosis with increasing frequency. It is important to correctly diagnose one of the monogenic forms of diabetes, as these children may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal treatment regimens and delays in diagnosing other family members.

The diagnosis of monogenic diabetes should be considered in children with the following situations:

- Diabetes diagnosed within the first six months of life.
- Strong family history of diabetes but without typical features of type 2 diabetes (nonobese, low-risk ethnic group).
- Mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), especially if young and nonobese.
- Diabetes but with negative auto-antibodies without signs of obesity or insulin resistance.

A recent international consensus document discusses in further detail the diagnosis and management of children with monogenic forms of diabetes (536).

B. Preconception Care

Recommendations

- A1C levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted. **B**
- Starting at puberty, preconception counseling should be incorporated in the routine diabetes clinic visit for all women of childbearing potential. **B**
- Women with diabetes who are contemplating pregnancy should be evaluated and, if indicated, treated for diabetic retinopathy, nephropathy, neuropathy, and CVD. **B**

- Medications used by such women should be evaluated prior to conception, since drugs commonly used to treat diabetes and its complications may be contraindicated or not recommended in pregnancy, including statins, ACE inhibitors, ARBs, and most noninsulin therapies. **E**
- Since many pregnancies are unplanned, consider the potential risks and benefits of medications that are contraindicated in pregnancy in all women of childbearing potential and counsel women using such medications accordingly. **E**

Major congenital malformations remain the leading cause of mortality and serious morbidity in infants of mothers with type 1 and type 2 diabetes. Observational studies indicate that the risk of malformations increases continuously with increasing maternal glycemia during the first 6–8 weeks of gestation, as defined by first-trimester A1C concentrations. There is no threshold for A1C values below which risk disappears entirely. However, malformation rates above the 1–2% background rate of nondiabetic pregnancies appear to be limited to pregnancies in which first-trimester A1C concentrations are >1% above the normal range for a nondiabetic pregnant woman.

Preconception Care

Preconception care of diabetes appears to reduce the risk of congenital malformations. Five nonrandomized studies compared rates of major malformations in infants between women who participated in preconception diabetes care programs and women who initiated intensive diabetes management after they were already pregnant. The preconception care programs were multidisciplinary and designed to train patients in diabetes self-management with diet, intensified insulin therapy, and SMBG. Goals were set to achieve normal blood glucose concentrations, and >80% of subjects achieved normal A1C concentrations before they became pregnant. In all five studies, the incidence of major congenital malformations in women who

participated in preconception care (range 1.0–1.7% of infants) was much lower than the incidence in women who did not participate (range 1.4–10.9% of infants) (104). One limitation of these studies is that participation in preconception care was self-selected rather than randomized. Thus, it is impossible to be certain that the lower malformation rates resulted fully from improved diabetes care. Nonetheless, the evidence supports the concept that malformations can be reduced or prevented by careful management of diabetes before pregnancy (537).

Planned pregnancies greatly facilitate preconception diabetes care. Unfortunately, nearly two-thirds of pregnancies in women with diabetes are unplanned, potentially leading to malformations in infants of diabetic mothers. To minimize the occurrence of these devastating malformations, beginning at the onset of puberty or at diagnosis, all women with diabetes with childbearing potential should receive 1) education about the risk of malformations associated with unplanned pregnancies and poor metabolic control and 2) use of effective contraception at all times, unless the patient has good metabolic control and is actively trying to conceive. A recent study showed that preconception counseling using simple educational tools enabled adolescent girls to make well-informed decisions lasting up to 9 months (538).

Women contemplating pregnancy need to be seen frequently by a multidisciplinary team experienced in diabetes management both before and during pregnancy. The goals of preconception care are to 1) involve and empower the patient on diabetes management, 2) achieve the lowest A1C test results possible without excessive hypoglycemia, 3) assure effective contraception until stable and acceptable glycemia is achieved, and 4) identify, evaluate, and treat long-term diabetes complications such as retinopathy, nephropathy, neuropathy, hypertension, and CHD (104).

Drugs Contraindicated in Pregnancy

Drugs commonly used in the diabetes treatment may be relatively or

absolutely contraindicated during pregnancy. Statins are category X (contraindicated for use in pregnancy) and should be discontinued before conception, as should ACE inhibitors (539). ARBs are category C (risk cannot be ruled out) in the first trimester but category D (positive evidence of risk) in later pregnancy and should generally be discontinued before pregnancy. Since many pregnancies are unplanned, health care professionals caring for any woman of childbearing potential should consider the potential risks and benefits of medications that are contraindicated in pregnancy. Women using medications such as statins or ACE inhibitors need ongoing family planning counseling. Among the oral antidiabetic agents, metformin and acarbose are classified as category B (no evidence of risk in humans) and all others as category C. Potential risks and benefits of oral antidiabetic agents in the preconception period must be carefully weighed, recognizing that data are insufficient to establish the safety of these agents in pregnancy.

For further discussion of preconception care, see the ADA consensus statement on preexisting diabetes and pregnancy (104) and the position statement (540).

C. Older Adults

Recommendations

- Older adults who are functional, cognitively intact, and have significant life expectancy should receive diabetes care with goals similar to those developed for younger adults. **E**
- Glycemic goals for some older adults might reasonably be relaxed, using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients. **E**
- Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials. **E**

- Screening for diabetes complications should be individualized in older adults, but particular attention should be paid to complications that would lead to functional impairment. **E**

Diabetes is an important health condition for the aging population; at least 20% of patients over the age of 65 years have diabetes, and this number can be expected to grow rapidly in the coming decades. Older individuals with diabetes have higher rates of premature death, functional disability, and coexisting illnesses such as hypertension, CHD, and stroke than those without diabetes. Older adults with diabetes are also at greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, depression, cognitive impairment, urinary incontinence, injurious falls, and persistent pain.

A consensus report on diabetes and older adults (541) influenced the following discussion and recommendations. The care of older

adults with diabetes is complicated by their clinical and functional heterogeneity. Some older individuals developed diabetes years earlier and may have significant complications; others who are newly diagnosed may have had years of undiagnosed diabetes with resultant complications or may have truly recent-onset disease and few or no complications. Some older adults with diabetes are frail and have other underlying chronic conditions, substantial diabetes-related comorbidity, or limited physical or cognitive functioning. Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable for this population, but often longer than clinicians realize. Providers caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals (**Table 15**).

There are few long-term studies in older adults demonstrating the benefits of intensive glycemic, blood pressure, and lipid control. Patients who can be

expected to live long enough to reap the benefits of long-term intensive diabetes management, who have good cognitive and functional function, and who choose to do so via shared decision making may be treated using therapeutic interventions and goals similar to those for younger adults with diabetes. As with all patients, DSME and ongoing DSMS are vital components of diabetes care for older adults and their caregivers.

For patients with advanced diabetes complications, life-limiting comorbid illness, or substantial cognitive or functional impairment, it is reasonable to set less intensive glycemic target goals. These patients are less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia. However, patients with poorly controlled diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. Glycemic goals at a minimum should avoid these consequences.

Table 15—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/ health status	Rationale	Reasonable A1C goal [‡]	Fasting or preprandial glucose (mg/dL)	Bedtime glucose (mg/dL)	Blood pressure (mmHg)	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5%	90–130	90–150	<140/80	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0%	90–150	100–180	<140/80	Statin unless contraindicated or not tolerated
Very complex/poor health (long-term care or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5% [†]	100–180	110–200	<150/90	Consider likelihood of benefit with statin (secondary prevention more so than primary)

This represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient/caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living. [‡]A lower goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, CHF, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse CKD, MI, and stroke. By multiple, we mean at least three, but many patients may have five or more (132). **The presence of a single end-stage chronic illness such as stage 3–4 CHF or oxygen-dependent lung disease, CKD requiring dialysis, or uncontrolled metastatic cancer may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. [†]A1C of 8.5% equates to an eAG of ~200 mg/dL. Looser glycemic targets than this may expose patients to acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

Although hyperglycemia control may be important in older individuals with diabetes, greater reductions in morbidity and mortality may result from control of other cardiovascular risk factors rather than from tight glycemic control alone. There is strong evidence from clinical trials of the value of treating hypertension in the elderly (542,543). There is less evidence for lipid-lowering and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the time frames seen in clinical trials.

Special care is required in prescribing and monitoring pharmacological therapy in older adults. Costs may be a significant factor, especially since older adults tend to be on many medications. Metformin may be contraindicated because of renal insufficiency or significant heart failure. Thiazolidinediones, if used at all, should be used very cautiously in those with, or at risk for, CHF, and have also been associated with fractures. Sulfonylureas, other insulin secretagogues, and insulin can cause hypoglycemia. Insulin use requires that patients or caregivers have good visual and motor skills and cognitive ability. DPP-4 inhibitors have few side effects, but their costs may be a barrier to some older patients; the latter is also the case for GLP-1 agonists.

Screening for diabetes complications in older adults also should be individualized. Particular attention should be paid to complications that can develop over short periods of time and/or that would significantly impair functional status, such as visual and lower-extremity complications.

D. Cystic Fibrosis–Related Diabetes

Recommendations

- Annual screening for CFRD with OGTT should begin by age 10 years in all patients with cystic fibrosis who do not have CFRD. **B** A1C as a screening test for CFRD is not recommended. **B**
- During a period of stable health, the diagnosis of CFRD can be made in cystic fibrosis patients according to usual glucose criteria. **E**
- Patients with CFRD should be treated with insulin to attain individualized glycemic goals. **A**

- Annual monitoring for complications of diabetes is recommended, beginning 5 years after the diagnosis of CFRD. **E**

CFRD is the most common comorbidity in persons with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults. Diabetes in this population is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality from respiratory failure. Insulin insufficiency related to partial fibrotic destruction of the islet mass is the primary defect in CFRD. Genetically determined function of the remaining β -cells and insulin resistance associated with infection and inflammation may also play a role. Encouraging data suggest that improved screening (544,545) and aggressive insulin therapy have narrowed the gap in mortality between cystic fibrosis patients with and without diabetes, and have eliminated the sex difference in mortality (546). Recent trials comparing insulin with oral repaglinide showed no significant difference between the groups. Insulin remains the most widely used therapy for CFRD (547).

Recommendations for the clinical management of CFRD can be found in the recent ADA position statement on this topic (548).

IX. DIABETES CARE IN SPECIFIC SETTINGS

A. Diabetes Care in the Hospital

Recommendations

- Diabetes discharge planning should start at hospital admission, and clear diabetes management instructions should be provided at discharge. **E**
- The sole use of sliding scale insulin in the inpatient hospital setting is discouraged. **E**
- All patients with diabetes admitted to the hospital should have their diabetes clearly identified in the medical record. **E**
- All patients with diabetes should have an order for blood glucose monitoring, with results available to all members of the health care team. **E**
- Goals for blood glucose levels:
 - **Critically ill patients:** Insulin therapy should be initiated for

treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL (10 mmol/L). Once insulin therapy is started, a glucose range of 140–180 mg/dL (7.8–10 mmol/L) is recommended for the majority of critically ill patients. **A**

- More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia. **C**
- Critically ill patients require an intravenous insulin protocol that has demonstrated efficacy and safety in achieving the desired glucose range without increasing risk for severe hypoglycemia. **E**
- **Non–critically ill patients:** There is no clear evidence for specific blood glucose goals. If treated with insulin, the premeal blood glucose targets generally <140 mg/dL (7.8 mmol/L) with random blood glucose <180 mg/dL (10.0 mmol/L) are reasonable, provided these targets can be safely achieved. More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be appropriate in those with severe comorbidities. **E**
- Scheduled subcutaneous insulin with basal, nutritional, and correctional components is the preferred method for achieving and maintaining glucose control in non–critically ill patients. **C**
- Glucose monitoring should be initiated in any patient not known to be diabetic who receives therapy associated with high risk for hyperglycemia, including high-dose glucocorticoid therapy, initiation of enteral or parenteral nutrition, or other medications such as octreotide or immunosuppressive medications. **B** If hyperglycemia is documented and persistent, consider treating such patients to the same glycemic goals as in patients with known diabetes. **E**
- A hypoglycemia management protocol should be adopted and

implemented by each hospital or hospital system. A plan for preventing and treating hypoglycemia should be established for each patient. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked. **E**

- Consider obtaining an A1C in patients with diabetes admitted to the hospital if the result of testing in the previous 2–3 months is not available. **E**
- Consider obtaining an A1C in patients with risk factors for undiagnosed diabetes who exhibit hyperglycemia in the hospital. **E**
- Patients with hyperglycemia in the hospital who do not have a prior diagnosis of diabetes should have appropriate plans for follow-up testing and care documented at discharge. **E**

Hyperglycemia in the hospital can represent previously known diabetes, previously undiagnosed diabetes, or hospital-related hyperglycemia (fasting blood glucose ≥ 126 mg/dL or random blood glucose ≥ 200 mg/dL occurring during the hospitalization that reverts to normal after hospital discharge). The difficulty distinguishing between the second and third categories during the hospitalization may be overcome by measuring an A1C in undiagnosed patients with hyperglycemia, as long as conditions interfering with A1C utility (hemolysis, blood transfusion) have not occurred. Hyperglycemia management in the hospital has been considered secondary in importance to the condition that prompted admission. However, a body of literature now supports targeted glucose control in the hospital setting for potential improved clinical outcomes. Hyperglycemia in the hospital may result from stress, decompensation of type 1 or type 2 or other forms of diabetes, and/or may be iatrogenic due to withholding of antihyperglycemic medications or administration of hyperglycemia-provoking agents such as glucocorticoids or vasopressors.

There is substantial observational evidence linking hyperglycemia in hospitalized patients (with or without

diabetes) to poor outcomes. Cohort studies as well as a few early RCTs suggested that intensive treatment of hyperglycemia improved hospital outcomes (549–551). In general, these studies were heterogeneous in terms of patient population, blood glucose targets and insulin protocols used, provision of nutritional support and the proportion of patients receiving insulin, which limits the ability to make meaningful comparisons among them. Trials in critically ill patients have failed to show a significant improvement in mortality with intensive glycemic control (552,553) or have even shown increased mortality risk (554). Moreover, these recent RCTs have highlighted the risk of severe hypoglycemia resulting from such efforts (552–557).

The largest study to date, NICE-SUGAR, a multicenter, multinational RCT, compared the effect of intensive glycemic control (target 81–108 mg/dL, mean blood glucose attained 115 mg/dL) to standard glycemic control (target 144–180 mg/dL, mean blood glucose attained 144 mg/dL) on outcomes among 6,104 critically ill participants, almost all of whom required mechanical ventilation (554). Ninety-day mortality was significantly higher in the intensive versus the conventional group in both surgical and medical patients, as was mortality from cardiovascular causes. Severe hypoglycemia was also more common in the intensively treated group (6.8% vs. 0.5%; $P < 0.001$). The precise reason for the increased mortality in the tightly controlled group is unknown. The study results lie in stark contrast to a 2001 single-center study that reported a 42% relative reduction in intensive care unit (ICU) mortality in critically ill surgical patients treated to a target blood glucose of 80–110 mg/dL (549). Importantly, the control group in NICE-SUGAR had reasonably good blood glucose management, maintained at a mean glucose of 144 mg/dL, only 29 mg/dL above the intensively managed patients. This study's findings do not disprove the notion that glycemic control in the ICU is important. However, they do strongly suggest that it may not be necessary to target blood glucose values

<140 mg/dL and that a highly stringent target of <110 mg/dL may actually be dangerous.

In a meta-analysis of 26 trials ($N = 13,567$), which included the NICE-SUGAR data, the pooled RR of death with intensive insulin therapy was 0.93 as compared with conventional therapy (95% CI 0.83–1.04) (557). Approximately half of these trials reported hypoglycemia, with a pooled RR of intensive therapy of 6.0 (95% CI 4.5–8.0). The specific ICU setting influenced the findings, with patients in surgical ICUs appearing to benefit from intensive insulin therapy (RR 0.63 [95% CI 0.44–0.91]), while those in other medical and mixed critical care settings did not. It was concluded that, overall, intensive insulin therapy increased the risk of hypoglycemia but provided no overall benefit on mortality in the critically ill, although a possible mortality benefit to patients admitted to the surgical ICU was suggested.

1. Glycemic Targets in Hospitalized Patients

Definition of Glucose Abnormalities in the Hospital Setting

Hyperglycemia in the hospital has been defined as any blood glucose >140 mg/dL (7.8 mmol/L). Levels that are significantly and persistently above this may require treatment in hospitalized patients. A1C values $>6.5\%$ suggest, in undiagnosed patients, that diabetes preceded hospitalization (558). Hypoglycemia has been defined as any blood glucose <70 mg/dL (3.9 mmol/L). This is the standard definition in outpatients and correlates with the initial threshold for the release of counter-regulatory hormones. Severe hypoglycemia in hospitalized patients has been defined by many as <40 mg/dL (2.2 mmol/L), although this is lower than the ~ 50 mg/dL (2.8 mmol/L) level at which cognitive impairment begins in normal individuals (559). Both hyper- and hypoglycemia among inpatients are associated with adverse short- and long-term outcomes. Early recognition and treatment of mild to moderate hypoglycemia (40–69 mg/dL [2.2–3.8 mmol/L]) can prevent deterioration to a more severe episode with potential adverse sequelae (560).

Critically Ill Patients

Based on the weight of the available evidence, for the majority of critically ill patients in the ICU setting, insulin infusion should be used to control hyperglycemia, with a starting threshold of no higher than 180 mg/dL (10.0 mmol/L). Once intravenous insulin is started, the glucose level should be maintained between 140 and 180 mg/dL (7.8 and 10.0 mmol/L). Greater benefit may be realized at the lower end of this range. Although strong evidence is lacking, lower glucose targets may be appropriate in selected patients. One small study suggested that ICU patients treated to targets of 120–140 had less negative nitrogen balance than those treated to higher targets (561). However, targets <110 mg/dL (6.1 mmol/L) are not recommended. Insulin infusion protocols with demonstrated safety and efficacy, resulting in low rates of hypoglycemia, are highly recommended (560).

Non–critically Ill Patients

With no prospective RCT data to inform specific glycemic targets in non–critically ill patients, recommendations are based on clinical experience and judgment (562). For the majority of non–critically ill patients treated with insulin, premeal glucose targets should generally be <140 mg/dL (7.8 mmol/L) with random blood glucose <180 mg/dL (10.0 mmol/L), as long as these targets can be safely achieved. To avoid hypoglycemia, consideration should be given to reassessing the insulin regimen if blood glucose levels fall below 100 mg/dL (5.6 mmol/L). Modifying the regimen is required when blood glucose values are <70 mg/dL (3.9 mmol/L), unless the event is easily explained by other factors (such as a missed meal). There is some evidence that systematic attention to hyperglycemia in the emergency room leads to better glycemic control in the hospital for those subsequently admitted (563).

Patients with a prior history of successful tight glycemic control in the outpatient setting who are clinically stable may be maintained with a glucose range below the aforementioned cut points. Conversely, higher glucose ranges may be acceptable in terminally ill patients or in patients with severe

comorbidities, as well as in those in patient-care settings where frequent glucose monitoring or close nursing supervision is not feasible.

Clinical judgment, combined with ongoing assessment of the patient's clinical status, including changes in the trajectory of glucose measures, the severity of illness, nutritional status, or concomitant medications that might affect glucose levels (e.g., steroids, octreotide) must be incorporated into the day-to-day decisions regarding insulin dosing (560).

2. Antihyperglycemic Agents in Hospitalized Patients

In most clinical situations in the hospital, insulin therapy is the preferred method of glycemic control (560). In the ICU, intravenous infusion is the preferred route of insulin administration. When the patient is transitioned off intravenous insulin to subcutaneous therapy, precautions should be taken to prevent hyperglycemia escape (564,565). Outside of critical care units, scheduled subcutaneous insulin that delivers basal, nutritional, and correctional (supplemental) components is recommended. Typical dosing schemes are based on body weight, with some evidence that patients with renal insufficiency should be treated with lower doses (566).

The sole use of sliding scale insulin is strongly discouraged in hospitalized patients. *A more physiological insulin regimen including basal, prandial, and correctional insulin is recommended.*

The insulin regimen must also incorporate prandial carbohydrate intake (567). For type 1 diabetic patients, dosing insulin solely based on premeal glucose would likely deliver suboptimal insulin doses and may potentially lead to DKA. It increases both hypoglycemia and hyperglycemia risks and has been shown in a randomized trial to be associated with adverse outcomes in general surgery patients with type 2 diabetes (568). The reader is referred to publications and reviews that describe currently available insulin preparations and protocols and provide guidance in use of insulin therapy in specific clinical settings including parenteral nutrition (569), enteral tube

feedings and with high dose glucocorticoid therapy (560).

There are no data on the safety and efficacy of oral agents and injectable noninsulin therapies such as GLP-1 analogs and pramlintide in the hospital. They appear to have a limited role in hyperglycemia management in conjunction with acute illness. Continuation of these agents may be appropriate in selected stable patients who are expected to consume meals at regular intervals. They may be initiated or resumed in anticipation of discharge once the patient is clinically stable. Specific caution is required with metformin, due to the possibility that a contraindication may develop during the hospitalization, such as renal insufficiency, unstable hemodynamic status, or need for an imaging study that requires a radiocontrast dye.

3. Preventing Hypoglycemia

Patients with or without diabetes may experience hypoglycemia in the hospital setting in association with altered nutritional state, heart failure, renal or liver disease, malignancy, infection, or sepsis. Additional triggering events leading to iatrogenic hypoglycemia include sudden reduction of corticosteroid dose, altered ability of the patient to report symptoms, reduced oral intake, emesis, new NPO status, inappropriate timing of short- or rapid-acting insulin in relation to meals, reduced infusion rate of intravenous dextrose, and unexpected interruption of enteral feedings or parenteral nutrition.

Despite the preventable nature of many inpatient episodes of hypoglycemia, institutions are more likely to have nursing protocols for hypoglycemia treatment than for its prevention. Tracking such episodes and analyzing their causes are important quality improvement activities (295).

4. Diabetes Care Providers in the Hospital

Inpatient diabetes management may be effectively championed and/or provided by primary care physicians, endocrinologists, intensivists, or hospitalists. Involvement of appropriately trained specialists or

specialty teams may reduce length of stay, improve glycemic control, and improve outcomes (560). Standardized orders for scheduled and correction-dose insulin should be implemented, and sole reliance on a sliding scale regimen strongly discouraged. As hospitals move to comply with “meaningful use” regulations for electronic health records, as mandated by the Health Information Technology Act, efforts should be made to assure that all components of structured insulin order sets are incorporated into electronic insulin order sets (570,571).

A team approach is needed to establish hospital pathways. To achieve glycemic targets associated with improved hospital outcomes, hospitals will need multidisciplinary support to develop insulin management protocols that effectively and safely enable achievement of glycemic targets (572).

5. Self-Management in the Hospital

Diabetes self-management in the hospital may be appropriate for competent youth and adult patients who have a stable level of consciousness and reasonably stable daily insulin requirements, successfully conduct self-management of diabetes at home, have physical skills needed to successfully self-administer insulin and perform SMBG, have adequate oral intake, are proficient in carbohydrate counting, use multiple daily insulin injections or insulin pump therapy, and understand sick-day management. The patient and physician, in consultation with nursing staff, must agree that patient self-management is appropriate while hospitalized.

Patients who use CSII pump therapy in the outpatient setting can be candidates for diabetes self-management in the hospital, provided that they have the mental and physical capacity to do so (560). A hospital policy and procedures delineating inpatient guidelines for CSII therapy are advisable, and availability of hospital personnel with expertise in CSII therapy is essential. It is important that nursing personnel document basal rates and bolus doses taken on a daily basis.

6. MNT in the Hospital

The goals of MNT are to optimize glycemic control, provide adequate

calories to meet metabolic demands, and create a discharge plan for follow-up care (551,573). The ADA does not endorse any single meal plan or specified percentages of macronutrients, and the term “ADA diet” should no longer be used. Current nutrition recommendations advise individualization based on treatment goals, physiological parameters, and medication use. Consistent carbohydrate meal plans are preferred by many hospitals since they facilitate matching the prandial insulin dose to the amount of carbohydrate consumed (574). Because of the complexity of nutrition issues in the hospital, a registered dietitian, knowledgeable and skilled in MNT, should serve as an inpatient team member. The dietitian is responsible for integrating information about the patient’s clinical condition, eating, and lifestyle habits and for establishing treatment goals in order to determine a realistic plan for nutrition therapy (116).

7. Bedside Blood Glucose Monitoring

Bedside POC blood glucose monitoring is used to guide insulin dosing. In the patient receiving nutrition, the timing of glucose monitoring should match carbohydrate exposure. In the patient not receiving nutrition, glucose monitoring is performed every 4–6 h (575,576). More frequent blood glucose testing ranging from every 30 min to every 2 h is required for patients on intravenous insulin infusions.

Safety standards should be established for blood glucose monitoring prohibiting sharing of finger-stick lancing devices, lancets, needles, and meters to reduce the risk of transmission of blood-borne diseases. Shared lancing devices carry essentially the same risk as sharing syringes and needles (577).

Accuracy of blood glucose measurements using POC meters has limitations that must be considered. Although the FDA allows a $\pm 20\%$ error for blood glucose meters, questions about the appropriateness of these criteria have been raised (388). Glucose measures differ significantly between plasma and whole blood, terms that are often used interchangeably and can lead to misinterpretation. Most

commercially available capillary blood glucose meters introduce a correction factor of ~ 1.12 to report a “plasma-adjusted” value (578).

Significant discrepancies between capillary, venous, and arterial plasma samples have been observed in patients with low or high hemoglobin concentrations, hypoperfusion, and the presence of interfering substances particularly maltose, as contained in immunoglobulins (579). Analytical variability has been described with several meters (580). Increasingly newer generation POC blood glucose meters correct for variation in hematocrit and for interfering substances. Any glucose result that does not correlate with the patient’s status should be confirmed through conventional laboratory sampling of plasma glucose. The FDA has become increasingly concerned about the use of POC blood glucose meters in the hospital and is presently reviewing matters related to their use.

8. Discharge Planning and DSME

Transition from the acute care setting is a high-risk time for all patients, not just those with diabetes or new hyperglycemia. Although there is an extensive literature concerning safe transition within and from the hospital, little of it is specific to diabetes (581). Diabetes discharge planning is not a separate entity, but is an important part of an overall discharge plan. As such, discharge planning begins at admission to the hospital and is updated as projected patient needs change.

Inpatients may be discharged to varied settings, including home (with or without visiting nurse services), assisted living, rehabilitation, or skilled nursing facilities. The latter two sites are generally staffed by health professionals, so diabetes discharge planning will be limited to communication of medication and diet orders. For the patient who is discharged to assisted living or to home, the optimal program will need to consider the type and severity of diabetes, the effects of the patient’s illness on blood glucose levels, and the capacities and desires of the patient. Smooth transition to outpatient care should be ensured. The Agency for Healthcare Research and Quality

recommends that, at a minimum, discharge plans include the following:

- **Medication reconciliation:** the patient's medications must be cross-checked to ensure that no chronic medications were stopped and to ensure the safety of new prescriptions.
- Prescriptions for new or changed medication should be filled and reviewed with the patient and family at or before discharge
- **Structured discharge communication:** Information on medication changes, pending tests and studies, and follow-up needs must be accurately and promptly communicated to outpatient physicians.
- Discharge summaries should be transmitted to the primary physician as soon as possible after discharge.
- Appointment keeping behavior is enhanced when the inpatient team schedules outpatient medical follow-up prior to discharge. Ideally the inpatient care providers or case managers/discharge planners will schedule follow-up visit(s) with the appropriate professionals, including primary care provider, endocrinologist, and diabetes educator (582).

Teaching diabetes self-management to patients in hospitals is a challenging task. Patients are ill, under increased stress related to their hospitalization and diagnosis, and in an environment not conducive to learning. Ideally, people with diabetes should be taught at a time and place conducive to learning: as an outpatient in a recognized program of diabetes education. For the hospitalized patient, diabetes "survival skills" education is generally a feasible approach to provide sufficient information and training to enable safe care at home. Patients hospitalized because of a crisis related to diabetes management or poor care at home require education to prevent subsequent episodes of hospitalization. Assessing the need for a home health referral or referral to an outpatient diabetes education program should be part of discharge planning for all patients.

DSME should start upon admission or as soon as feasible, especially in those new to insulin therapy or in whom the diabetes regimen has been substantially altered during the hospitalization.

It is recommended that the following areas of knowledge be reviewed and addressed prior to hospital discharge:

- Identification of the health care provider who will provide diabetes care after discharge
- Level of understanding related to the diagnosis of diabetes, SMBG, and explanation of home blood glucose goals
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia
- Information on consistent eating patterns
- When and how to take blood glucose-lowering medications including insulin administration (if going home on insulin)
- Sick-day management
- Proper use and disposal of needles and syringes

It is important that patients be provided with appropriate durable medical equipment, medication, supplies and prescriptions at the time of discharge in order to avoid a potentially dangerous hiatus in care. These supplies/prescriptions should include the following:

- Insulin (vials or pens) if needed
- Syringes or pen needles (if needed)
- Oral medications (if needed)
- Blood glucose meter and strips
- Lancets and lancing device
- Urine ketone strips (type 1)
- Glucagon emergency kit (insulin treated)
- Medical alert application/charm

More expanded diabetes education can be arranged in the community. An outpatient follow-up visit with the primary care provider, endocrinologist, or diabetes educator within 1 month of discharge is advised for all patients having hyperglycemia in the hospital. Clear communication with outpatient providers either directly or via hospital discharge summaries facilitates safe transitions to outpatient care. Providing information regarding the cause or the

plan for determining the cause of hyperglycemia, related complications and comorbidities, and recommended treatments can assist outpatient providers as they assume ongoing care.

B. Diabetes and Employment

Any person with diabetes, whether insulin treated or noninsulin treated, should be eligible for any employment for which he or she is otherwise qualified. Employment decisions should never be based on generalizations or stereotypes regarding the effects of diabetes. When questions arise about the medical fitness of a person with diabetes for a particular job, a health care professional with expertise in treating diabetes should perform an individualized assessment. See the ADA position statement on diabetes and employment (583).

C. Diabetes and Driving

A large percentage of people with diabetes in the U.S. and elsewhere seek a license to drive, either for personal or employment purposes. There has been considerable debate whether, and the extent to which, diabetes may be a relevant factor in determining the driver ability and eligibility for a license.

People with diabetes are subject to a great variety of licensing requirements applied by both state and federal jurisdictions, which may lead to loss of employment or significant restrictions on a person's license. Presence of a medical condition that can lead to significantly impaired consciousness or cognition may lead to drivers being evaluated for fitness to drive. For diabetes, this typically arises when the person has had a hypoglycemic episode behind the wheel, even if this did not lead to a motor vehicle accident.

Epidemiological and simulator data suggest that people with insulin-treated diabetes have a small increase in risk of motor vehicle accidents, primarily due to hypoglycemia and decreased awareness of hypoglycemia. This increase (RR 1.12–1.19) is much smaller than the risks associated with teenage male drivers (RR 42), driving at night (RR 142), driving on rural roads

compared with urban roads (RR 9.2), and obstructive sleep apnea (RR 2.4), all of which are accepted for unrestricted licensure.

The ADA position statement on diabetes and driving (584) recommends against blanket restrictions based on the diagnosis of diabetes and urges individual assessment by a health care professional knowledgeable in diabetes if restrictions on licensure are being considered. Patients should be evaluated for decreased awareness of hypoglycemia, hypoglycemia episodes while driving, or severe hypoglycemia. Patients with retinopathy or peripheral neuropathy require assessment to determine if those complications interfere with operation of a motor vehicle. Health care professionals should be cognizant of the potential risk of driving with diabetes and counsel their patients about detecting and avoiding hypoglycemia while driving.

D. Diabetes Management in Correctional Institutions

People with diabetes in correctional facilities should receive care that meets national standards. Because it is estimated that nearly 80,000 inmates have diabetes, correctional institutions should have written policies and procedures for the management of diabetes and for training of medical and correctional staff in diabetes care practices. See the ADA position statement on diabetes management in correctional institutions (585) for further discussion.

X. STRATEGIES FOR IMPROVING DIABETES CARE

Recommendations

- Care should be aligned with components of the Chronic Care Model (CCM) to ensure productive interactions between a prepared proactive practice team and an informed activated patient. **A**
- When feasible, care systems should support team-based care, community involvement, patient registries, and embedded decision support tools to meet patient needs. **B**
- Treatment decisions should be timely and based on evidence-based guidelines that are tailored to individual patient preferences, prognoses, and comorbidities. **B**
- A patient-centered communication style should be used that incorporates patient preferences, assesses literacy and numeracy, and addresses cultural barriers to care. **B**

There has been steady improvement in the proportion of diabetic patients achieving recommended levels of A1C, blood pressure, and LDL cholesterol in the last 10 years, both in primary care settings and in endocrinology practices. Mean A1C nationally has declined from 7.82% in 1999–2000 to 7.18% in 2004 based on NHANES data (586). This has been accompanied by improvements in lipids and blood pressure control and led to substantial reductions in end-stage microvascular complications in those with diabetes. Nevertheless, between 33.4 to 48.7% of patients with diabetes still do not meet targets for glycemic, blood pressure, and cholesterol control, and only 14.3% meet targets for the combination of all three measures and nonsmoking status (317). Evidence also suggests that progress in risk factor control (particularly tobacco use) may be slowing (317,587). Certain patient groups, such as patients with complex comorbidities, financial or other social hardships, and/or limited English proficiency, may present particular challenges to goal-based care (588,589). Persistent variation in quality of diabetes care across providers and across practice settings even after adjusting for patient factors indicates that there remains potential for substantial further improvements in diabetes care.

While numerous interventions to improve adherence to the recommended standards have been implemented, a major barrier to optimal care is a delivery system that too often is fragmented, lacks clinical information capabilities, often duplicates services, and is poorly designed for the coordinated delivery of chronic care. The CCM has been shown to be an effective framework for improving the quality of diabetes care (590). The CCM includes six core elements for the provision of optimal care of patients

with chronic disease: 1) delivery system design (moving from a *reactive* to a *proactive care* delivery system where planned visits are coordinated through a team-based approach, 2) self-management support, 3) decision support (basing care on evidence-based, effective care guidelines), 4) clinical information systems (using registries that can provide patient-specific and population-based support to the care team), 5) community resources and policies (identifying or developing resources to support healthy lifestyles), and 6) health systems (to create a quality-oriented culture). Redefinition of the roles of the clinic staff and promoting self-management on the part of the patient are fundamental to the successful implementation of the CCM (591). Collaborative, multidisciplinary teams are best suited to provide such care for people with chronic conditions such as diabetes and to facilitate patients' performance of appropriate self-management (222,224,287,592).

NDEP maintains an online resource (www.betterdiabetescare.nih.gov) to help health care professionals design and implement more effective health care delivery systems for those with diabetes. Three specific objectives, with references to literature that outlines practical strategies to achieve each, are outlined below.

Objective 1: Optimize Provider and Team Behavior

The care team should prioritize timely and appropriate intensification of lifestyle and/or pharmaceutical therapy of patients who have not achieved beneficial levels of blood pressure, lipid, or glucose control (593). Strategies such as explicit goal setting with patients (594); identifying and addressing language, numeracy, or cultural barriers to care (595–598); integrating evidence-based guidelines and clinical information tools into the process of care (599–601); and incorporating care management teams including nurses, pharmacists, and other providers (602–604) have each been shown to optimize provider and team behavior and thereby catalyze reduction in A1C, blood pressure, and LDL cholesterol.

Objective 2: Support Patient Behavior Change

Successful diabetes care requires a systematic approach to supporting patients' behavior change efforts, including 1) healthy lifestyle changes (physical activity, healthy eating, nonuse of tobacco, weight management, effective coping); 2) disease self-management (medication taking and management and self-monitoring of glucose and blood pressure when clinically appropriate); and 3) prevention of diabetes complications (self-monitoring of foot health; active participation in screening for eye, foot, and renal complications; and immunizations). High-quality DSME has been shown to improve patient self-management, satisfaction, and glucose control (242,605), as has delivery of ongoing DSMS, so that gains achieved during DSME are sustained (606–608). National DSME standards call for an integrated approach that includes clinical content and skills, behavioral strategies (goal setting, problem solving) and addressing emotional concerns in each needed curriculum content area.

Objective 3: Change the System of Care

The most successful practices have an institutional priority for providing high quality of care (609). Changes that have been shown to increase quality of diabetes care include basing care on evidence-based guidelines (610), expanding the role of teams and staff (602,611), redesigning the processes of care (612), implementing electronic health record tools (613,614), activating and educating patients (615,616), and identifying and/or developing and engaging community resources and public policy that support healthy lifestyles (617). Recent initiatives such as the Patient-Centered Medical Home show promise to improve outcomes through coordinated primary care and offer new opportunities for team-based chronic disease care (618). Alterations in reimbursement that reward the provision of appropriate and high-quality care rather than visit-based billing (619) and that can accommodate the need to personalize care goals may provide additional

incentives to improve diabetes care (620).

It is clear that optimal diabetes management requires an organized, systematic approach and involvement of a coordinated team of dedicated health care professionals working in an environment where patient-centered high-quality care is a priority.

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