2019 FMX Endocrine Handouts

(PBL) Diabetes Treatment Update: After Metformin (CME046-047)

(PBL) Prediabetes Screening and Management: A Spoonful of Prevention! Get Ahead of Diabetes (CME048-049)

Adult Obesity Management: Weight Loss Counseling Made Easy (CME050-051)

Childhood Growth and Puberty Delay Disorders (CME060-061)

Diabetes Treatment Update: After Metformin (CME052-053)

Endocrine Disorders in Pregnancy (CME062-063)

Hyperthyroidism and Hypothyroidism: The Ups and Downs (CME054-055)

Prediabetes Screening and Management: A Spoonful of Prevention! Get Ahead of Diabetes (CME056-057)

Vitamin Deficiencies: Common Nutrient Deficiencies in Practice (CME058-059)
(PBL) Diabetes Treatment Update: After Metformin

Barbara Keber, MD, FAAFP
Mary Muscarello, MSN, ANP-C, CDE, CRRN

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Barbara Keber, MD, FAAFP

Physician, Northwell Health Physician Partners Family Medicine, Glen Cove, New York; Vice Chair/Associate Professor of Family Medicine, Department of Family Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; Chair of Family Medicine, Glen Cove Hospital, New York

Dr. Keber earned her medical degree from the State University of New York (SUNY) Downstate College of Medicine, Brooklyn, and completed her residency in family medicine at the Community Hospital of Glen Cove, New York. She has been a board-certified family physician for 35 years and currently works for Northwell Health Physician Partners Family Medicine at Glen Cove Hospital. For the past five years, the combined faculty and residency practice has had National Committee for Quality Assurance (NCQA) recognition as a Level 3 Patient-Centered Medical Home (PCMH), and Dr. Keber has been instrumental in developing the patient-centered approach and team-based care. In addition, she is the physician leader for the diabetes program in both the inpatient and ambulatory settings. She is currently the physician lead for the Enterprise Diabetes Project for the Northwell Health System, leading efforts to enhance and standardize diabetes care within the enterprise. She has lectured on topics related to diabetes care/management and team-based population health within the PCMH model of care.
Mary Muscarello, MSN, ANP-C, CDE, CRRN

Nurse Practitioner/Outpatient Diabetes Self-Management Program Coordinator/Inpatient Diabetes Educator, Glen Cove Hospital, New York

Muscarello earned her Bachelor of Science (BS) degree in nursing from Molloy College in Rockville Centre, New York, and her master’s degree in adult health from Stony Brook University, New York. For more than 17 years, she has worked for Northwell Health in various positions, including acute rehab, and as a visiting nurse. A board-certified adult nurse practitioner and certified diabetes educator, she currently works in a hospital-based family medicine clinic, specializing in the care of patients who have diabetes. She works with a socioeconomically disadvantaged population, comprised mostly of immigrants from Central America who have limited English proficiency and limited financial resources. Because many of them have never attended school, literacy and numeracy are major challenges for Muscarello’s patients. She uses numerous hands-on tools to enhance her patients’ understanding of their condition and treatment. She believes that the marriage of evidence-based medicine, shared decision-making, and relationship-based care makes all the difference in successfully getting patients to goal. She has been nominated for and received several awards, including the Northwell Health President’s Award for Exceptional Patient/Customer Experience for the Eastern Region.

Learning Objectives

1. Practice applying new knowledge and skills gained from Diabetes Treatment and Update sessions, through collaborative learning with peers and expert faculty.

2. Identify strategies that foster optimal management of diabetes treatment within the context of professional practice.

3. Formulate an action plan to implement practice changes, aimed at improving patient care.
Associated Sessions

- Diabetes Treatment Update: After Metformin

What are your goals? For your patients??
We Should Aim for Treatment That Fits

Scary Fact:

Studies have shown that 40-80% of the medical information patients are told in a medical appointment is forgotten immediately, and nearly half of the information that is retained is remembered incorrectly.
Providing Patient-Centered Care

- **Important things to consider:**
  - Patient’s health beliefs and cultural traditions
  - Literacy and numeration
  - Cognitive and physical abilities
  - Personal preferences and values
  - Family situations and support
  - Patient lifestyle
  - Financial limitations
  - Patient willingness

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Adherence

- Lack of perceived severity
- Affordability
- Complexity of regime
- Competing factors
- Hypoglycemia and other side effects
- Using incorrectly
- One and done? Stopping existing med when new med added?
Case 1 JS

• 69 year old male
• Type 2 Diabetes x 13 years
• OSA
• HTN
• Grade 2 Diastolic Heart Failure
• Obesity
• Does not exercise

Medications

• amlodipine 5 mg daily
• aspirin 81 mg daily
• atorvastatin 20 mg daily
• losartan 25 mg daily
• metformin 500 mg BID (unable to tolerate 1,000 mg BID)
Labs

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<tr>
<td>eGFR</td>
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Blood Glucose Testing at Home

- Rarely tested at home
- Fasting 110-134
- Bedtime 175-230
Small Group Case 1 Discussion

- What if anything would you change?
- What follow up should you do?
- When would you follow up?
- Is there any other team member you want to involve to assist you?

Case 2 MJ

- 54 year old female
- Morbidly obese, BMI 42.5
- Hypertension
- HLD
- Type 2 Diabetes x 5 years
- Lives with spouse and 2 children
### Labs

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<td>LDL</td>
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<td>Triglycerides</td>
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### Medications

- Metformin 1,000 mg BID
- Lisinopril 20 mg daily
- Amlodipine 5 mg daily
- Refuses statins
- Refusing insulin
- GLP1 Semaglutide 1.5 mg weekly added Oct. 2018
Case 2 MJ Blood Glucose Testing

- Sporadically testing
- Often “forgets”
- Tests on “good” days
- Stops testing when high readings seen
- Range 150-325

Small Group Case 2 Discussion

- What do you do next?
- How do you get this patient to understand the issues?
- This patient thinks she can do this with just her diet- how do you convince her this will not correct her blood sugar?
- What points need discussion and who can help you to work with her?
Case 3 JW

- 74 year old male, recently retired, lives alone
- Type 2 Diabetes x 12 years
- HTN, variably controlled
- Overweight, BMI 29.9
- Sedentary due to DJD of hip and recent hip replacement
- Diagnosed with Coronary Artery Disease at age 71
- Irregular eating habits, often skips meals

**Labs**

<table>
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<tr>
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<td>Triglycerides</td>
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Medication

- Metformin 1,000 mg BID
- Sitagliptin 100 mg daily
- Atorvastatin 20 mg QHS
- Lisinopril 10 mg daily
- Co-Q 10 200 mg QHS
- Vitamin D 2,000 mg daily

BG Testing

- Fasting 120-160
- Only willing to test once daily

Case 3 Group Discussion

- What options are available currently to reduce the A1C?
- What reasons do you have for making a particular choice?
- Is there any other information you want to have before making a decision on the next steps?
Case 4 LB

- 76 year old, obese (BMI 32) female
- Variably controlled Type 2 x 18 years
- HTN
- HLD
- CAD diagnosed 5 years ago with 2 cardiac stents placed
- 2 additional stents 2 years later

Case 4 Medications

- Metformin 1,000 mg BID
- Sitagliptin 100 mg daily
- Aspirin 81 mg daily
- Atorvastatin 40 mg QHS
- Metoprolol 25 mg BID
- Losartan 50 mg daily
Labs

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<tr>
<td>eGFR</td>
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Case 4 Discussion

- What options are currently available to improve the control of her diabetes?
- Why would you choose or not choose a particular agent?
- How much improvement in the A1C do you anticipate with the proposed change?
Summary

- Always assess medication adherence – don’t increase meds not taken
- Assess patient willingness for prescribed treatment
- Don’t underestimate effectiveness of lifestyle changes
- Always refer for MNT and DSME
- Consider SGLT2 inhibitors (renal and heart failure indications)
- Consider GLP1 RA when weight loss indicated with or without CV disease
- DPP 4 inhibitors- not to be used with GLP1RA – similar mechanism of action and no proven additional benefits for CV disease or renal disease

Contact Information

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- Mary Muscarello
  - mmuscarel@northwell.edu
Questions

Referrences

• ACCE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2019 January 2019


• Diabetes Care January 2019 Volume 42, Supplement 1 American Diabetes Association Standards of Care 2019, online version updated as of June 2019 https://doi.org/10.2337/dc19-S101

• Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2019, American Diabetes Association, Diabetes Care 2018 Jan; 42(Supplement 1): S73-S85.
(PBL) Prediabetes Screening and Management: A Spoonful of Prevention!
Get Ahead of Diabetes

Kate Kirley, MD, MS
Janet Williams, MA

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The prediabetes will include discussion of Metformin for the indication of prediabetes treatment. This is a non-FDA approved (off-label) use of Metformin despite high quality evidence of efficacy and safety.

Kate Kirley, MD, MS

Director of Chronic Disease Prevention, Improving Health Outcomes group, American Medical Association (AMA), Chicago, Illinois

After graduating from the University of Michigan Medical School, Ann Arbor, Dr. Kirley completed her family medicine residency at the University of Illinois at Chicago (UIC)/Illinois Masonic Medical Center. She subsequently completed a research fellowship at the University of Chicago. Currently, she serves as the lead clinician for the AMA’s diabetes prevention initiatives. Prior to joining the AMA, Dr. Kirley was a practicing family physician and health services researcher at NorthShore University HealthSystem, and a clinical assistant professor in the University of Chicago’s Department of Family Medicine. She also served as assistant director of NorthShore’s Quality and Patient Safety Fellowship and as assistant director of the Ambulatory Primary Care Innovations Group, a practice-based research network.
Janet Williams, MA

Senior Program Manager, Physician and Health System Engagement, Improving Health Outcomes, American Medical Association, Chicago, Illinois

Williams manages the American Medical Association’s (AMA’s) prediabetes initiative to develop and test clinical tools and resources for engaging health systems, clinicians, and health departments in diabetes prevention. She works with health system leadership and clinical practices to establish a prediabetes screening and referral mechanism that is integrated into existing clinical care. Before joining the AMA, she was director of tobacco prevention and control for the Cook County Department of Public Health and deputy executive director of public affairs for the American Lung Association of Metropolitan Chicago.

Williams has more than 30 years of public health program and policy development experience. She regularly presents on clinical practice change and improving prevention at the clinical and community levels. Her speaking engagements have included conferences hosted by the American Public Health Association (APHA), Institute for Healthcare Improvement (IHI), Cardiometabolic Health Congress, and American Hospital Association (AHA). She has an undergraduate degree from the School of the Art Institute of Chicago and a master’s degree in media advocacy and public policy from DePaul University, Chicago, Illinois.

Learning Objectives

1. Practice applying new knowledge and skills gained from Prediabetes Screening and Management sessions, through collaborative learning with peers and expert faculty.

2. Identify strategies that foster optimal management of prediabetes within the context of professional practice.

3. Formulate an action plan to implement practice changes, aimed at improving patient care.
Associated Sessions

• Prediabetes Screening and Management: A Spoonful of Prevention! Get Ahead of Diabetes
Diabetes Prevention Program RCT

- NIH-funded 3-arm RCT (N=3234) comparing placebo vs metformin vs intensive lifestyle counseling
  - Low calorie, low fat diet plus moderate physical activity
  - Program goal: ≥7% weight loss
- The lifestyle intervention reduced the incidence by 58% compared to placebo
  - Metformin reduced the incidence by 31% compared to placebo

Figure 2. Cumulative Incidence of Diabetes According to Study Group.


United States Preventive Services Task Force (USPSTF)

Abnormal Glucose Screening Recommendation

Offer or refer patients with abnormal glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity
Metformin

- Not FDA-approved for diabetes prevention
- High-quality evidence demonstrates effectiveness
- Consider in those with
  - BMI $\geq 35$ kg/m$^2$
  - Age <60
  - Women with h/o GDM
  - Worsening glucose despite lifestyle intervention


Role Play Round 1
Shared Decision Making

• Collaborative process
• Arrive at a decision mutually agreeable to patient and clinician
• Informed by patient’s values and preferences

Why SDM Makes Sense for Prediabetes

• More than one reasonable option exists
• Options are easy to define in lay terms
• Pros/cons of each option identify patient preference
Six Steps of SDM

1. Invite the patient to participate
2. Present options
3. Provide information on benefits and risks
4. Assist patients in evaluating options based on their goals and concerns
5. Facilitate deliberation and decision making
6. Assist patients to follow through on the decision


Keys to a Good Decision Aid

• Provide information in sufficient detail for decision making
• Present outcomes in unbiased and understandable language
• Include methods for clarifying patient and values
Intensive Lifestyle Change Program

Metformin

Role Play Round 2

Discussion

• How were the two rounds of role playing different?
Discussion

• How do you navigate when the most effective option may not be the patient’s chosen option?

Discussion

• How would you approach these patients over the long-term?
Questions
Childhood Growth and Puberty Delay Disorders

MAJ Craig Barstow, MD

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MAJ Craig Barstow, MD

Director of Hospital Medicine, Womack Army Medical Center, Fort Bragg, North Carolina; Assistant Professor of Family Medicine at Uniformed Services University of Health Sciences, Bethesda, Maryland; Director of Ultrasound Education, Family Medicine Residency Program, Womack Army Medical Center; Physician, Scotland Memorial Hospital Emergency Department, Laurinburg, North Carolina

Dr. Barstow is a graduate of the Uniformed Services University of the Health Sciences – F. Edward Herbert School of Medicine in Bethesda, Maryland. He completed undergraduate studies at the U.S. Military Academy. Dr. Barstow joined the Womack Army Medical Center Family Medicine Residency Program in 2012, and created the fellowship program, accepting the first fellow in July 2015. He is the former program director of the hospitalist fellowship at Womack Army Medical Center. His areas of interest include inpatient family medicine, newborn care, and point-of-care ultrasound teaching.
Learning Objectives

1. Establish evidence-based protocols for evaluating pediatric patients for growth and pubertal delay.

2. Consider biases that lead to gender differences in the evaluation and treatment of short stature.

3. Counsel patients regarding the safety, efficacy, cost, risks, and benefits of available treatment options.

4. Develop individualized treatment therapy, and coordinate care as appropriate.

Audience Engagement System

Step 1

Step 2

Step 3
Agenda

1. Failure to Thrive
2. Short Stature
3. Tall Stature
4. Delayed Puberty

Failure to Thrive
Case 1

A 9-month old male infant is brought in by his mother for a well child visit. He is healthy appearing and developmentally normal. He is primarily breast fed but his mother has introduced table foods. When you plot his weight on the CDC growth curve, his weight is below the 5th percentile. The physical exam is normal and the review of symptoms is negative.

CDC Growth Chart
Poll Question 1

What is your next, best step?

A. Conduct a detailed nutritional history
B. Plot the infant on the WHO growth chart
C. Order labs for celiac disease
D. Admit to infant for a failure to thrive work up

Which Growth Chart to Use?

2000 CDC Growth Chart
- Data from various sources (NHANES and others)
- Cross-sectional data
- 50% were ever breastfed
- 33% breastfed at 3 months

WHO Growth Chart
- Data from WHO Multicentre Growth Reference Study
- Prospective study of 882 children
- 100% were ever breastfed
- 100% breastfed through 12 months

Which Growth Chart to Use?

- MGRS established standards for healthy children under optimal conditions
- CDC established a reference for how certain children grow in a certain place
- Breast feeding is recommended standard for infant feeding
- Fewer US children are identified as underweight on WHO charts

Recommendations

- Use 2006 WHO growth charts for children < 24 months of age
- Use the 2000 CDC growth charts for children 25-59 months
- Use 2.3rd and 97.7th percentile to define abnormal growth (2 standard deviations)

Breast Feeding vs. Bottle Feeding

- Gain weight faster in the first 3 months
- Gain weight more slowly for the remainder of infancy
Case 2

A 6-week old infant is brought to your office by her mother. She recently visited relatives who noted the infant was small and thin appearing. The child is exclusively breast fed. The pregnancy was unremarkable and the infant was AGA at birth. At two weeks, he had surpassed his birth weight. At today’s visit, his weight is 350 grams less than it was 4 weeks ago and his weight vs. age is < 2.5th percentile.
Poll Question 2

Which of the following are consistent with normal growth for an infant?

A. Lose 10% of body weight after birth
B. Regain birth weight within 7 days
C. Double birth weight by 4-6 months
D. Triple birth weight by 1 year
E. All of the above

Normal Growth Infants

• Lose up to 10% of birth weight
• Regain birth weight within 7 days
• Double weight by 4-6 months
• Triple weight by 1 year

Failure to Thrive

- Abnormal pattern of weight gain
- Insufficient nutrition
  - Inadequate caloric intake
  - Inadequate caloric absorption
  - Increased metabolism
- “Weight faltering”


Failure to Thrive

Progressive loss of growth
- Weight
- Length
- Head circumference
Failure to Thrive - Evaluation

- History: focus on nutrition
- Physical exam
  - Acute or chronic illness
  - Signs of genetic condition
  - Evaluate development
- Plot growth over multiple visits

Failure to Thrive - Evaluation

- Diagnosis is usually made by history and physical
- Laboratory evaluation should be guided by H&P
  - Complete blood count
  - Urinalysis
  - Electrolytes
  - Thyroid function
  - Celiac disease
Failure to Thrive

Inadequate caloric intake (most common cause)
• Gastroesophageal reflux
• Inadequate breast milk supply or ineffective latching
• Incorrect formula preparation
• Mechanical feeding difficulties
• Neglect or abuse
• Poor feeding habits


Failure to Thrive

Inadequate nutrient absorption
• Iron deficiency anemia
• Biliary atresia
• Celiac disease
• Chronic GI conditions
• Cystic fibrosis
• Inborn errors of metabolism
• Milk protein allergy

Failure to Thrive

Increased metabolism
• Chronic infection (HIV, tuberculosis)
• Chronic lung disease
• Congenital heart disease
• Hyperthyroidism
• Inflammatory conditions
• Malignancy
• Renal failure


Evaluation of Breastfeeding

• Pre- and post-feed weights
• Lactation consultation
• Consider supplementation with formula
Case 2 Continued

William and his mother were referred to lactation. Evaluation showed a decreased production of breast milk. The mother was instructed to breast feed for 30 minutes then supplement with formula as tolerated. She was also prescribed a hospital-grade breast pump and encouraged to pump after each breastfeeding. Over the next week the patient gained 48 grams per day.

Normal Weight Gain in Children

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<tr>
<td>12 and older</td>
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- Catch-up growth is two-three times average rate.

Case 2 Continued

Upon recommendation of the lactation consultant, William was switched to an increased caloric formula for supplementation. Six days later he had gained an average of 83 grams per day. By 4 months of age, his weight vs. age was in the 56th percentile.
Dietary Reference Intake

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<td>6 to 12 months</td>
<td>98</td>
</tr>
<tr>
<td>1 to 3 years</td>
<td>102</td>
</tr>
</tbody>
</table>


Catch-up caloric requirements

- Take 50th percentile weight (ideal weight) for age from growth chart
- Multiply ideal weight by Dietary Reference Intake (DRI) for age
- Result is daily caloric catch-up requirement

Catch-up caloric requirements
Example

• 50th percentile weight for a 3-month old boy is 13 kg
• Dietary Reference Intake (DRI) for 3-months is 108 kcal/kg/day
• Daily caloric catch-up requirement is
  \[ 13 \text{ kg} \times 108 \text{ kcal/kg/day} = 1,404 \text{ kcal/day} \]

Formula Recipes

<table>
<thead>
<tr>
<th>Calories (kcal) per oz</th>
<th>Water (oz)</th>
<th>Scoops of formula powder</th>
<th>Final volume (oz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>4</td>
<td>2</td>
<td>4 1/2</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>2</td>
<td>4 1/2</td>
</tr>
<tr>
<td>22</td>
<td>3.5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>3</td>
<td>5.5</td>
</tr>
<tr>
<td>26</td>
<td>3</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>27</td>
<td>7</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

Case 3

Mariah is a 9 month infant who has failed to gain adequate weight. Over the course of 3 visits, she has continued to fall off the growth chart. Her current weight vs. age is 0 percentile. Her mother suffers from post-partum depression and has missed several scheduled office visits for Mariah. On this visit, her length has begun to fall of the growth curve.

Indications for Hospitalization

• Extreme parental impairment or anxiety
• Extremely poor parent-child interaction
• Need to precisely document nutritional intake
• Outpatient treatment failure
• Severe malnutrition or dehydration
Red Flags

Consider further evaluation if failure to thrive is not isolated finding
• Developmental delay
• Hypotonia
• Neurological symptoms
• Recurrent vomiting
• Liver dysfunction
• Shortness of breath/difficulty feeding
• Acidosis


Short Stature
Case 4

Ryan is a 10-year old boy who is brought to your office for his annual well child exam. You plot him at the 2\textsuperscript{nd} percentile for height and the 10\textsuperscript{th} percentile for weight. His parents are concerned that he is shorter than all of his classmates and wonder if Ryan should see a pediatric endocrinologist.

Poll Question 3

Which of the following causes of short stature are considered normal variants?

A. Constitutional delay of growth and puberty
B. Familial short stature
C. Idiopathic short stature
D. All of the above
Normal Growth

• Newborn size is a result of intrauterine environment
• Catch up (or catch down) growth between six and 18 months of age
• Reach genetically determine growth curve
  • Mid-parental height
  • Children track along percentile (+/- two large bands)
• Growth hormone predominant role after 2 years of age
• At adolescence, growth increases at puberty
  • Sex hormones predominant role

Short Stature

Defined as a height more than two standard deviations (less than 3rd percentile) below the mean for age

Most children will have a normal variant
• Familial short stature
• Constitutional delay of growth and puberty
• Idiopathic short stature
Poll Question 4

What percentage of children referred for evaluation of short stature will have an identifiable, pathological cause?

A. 25%
B. 15%
C. 5%
D. < 1%

Short Stature

5% of children referred for evaluation of short stature will have an identifiable pathological cause
• Growth hormone deficiency
• Hypothyroidism
• Celiac disease
• Turner syndrome

Short Stature – Initial Evaluation

- History and physical evaluation
- Accurate growth assessment
- Calculate growth velocity
- Bone age evaluation

History and Physical Evaluation

- Chronic disease
- Renal, hepatic or gastrointestinal complaints
- Medication history
- Dysmorphic features
Accurate Growth Assessment

• Use appropriate growth charts
• Correctly measure the child
• Plot growth at every visit
• Obtain two measurements at least 3-6 months apart
• Calculate growth velocity

Mid-parental Height

Girls
• \[
\frac{\text{Paternal height (in)} - 5 \text{ in} + \text{maternal height (in)}}{2}
\]

Boys
• \[
\frac{\text{Paternal height (in)} + 5 \text{ in} + \text{maternal height (in)}}{2}
\]

Most children have a projected height within 4 inches of mid-parental height
Normal Growth Velocity by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Growth Velocity (per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 12 months</td>
<td>23 to 27 cm (9.06 to 10.63 in)</td>
</tr>
<tr>
<td>12 months to 1 year</td>
<td>10 to 14 cm (3.94 to 5.51 in)</td>
</tr>
<tr>
<td>2 to 3 years</td>
<td>8 cm (3.15 in)</td>
</tr>
<tr>
<td>3 to 5 years</td>
<td>7 cm (2.76 in)</td>
</tr>
<tr>
<td>5 years to puberty</td>
<td>5 to 6 cm (1.97 to 2.36 in)</td>
</tr>
<tr>
<td>Puberty</td>
<td></td>
</tr>
<tr>
<td>Girls: 8 to 12 cm</td>
<td>(3.15 to 4.72 in)</td>
</tr>
<tr>
<td>Boys: 10 to 14 cm</td>
<td>(3.94 to 5.51 in)</td>
</tr>
</tbody>
</table>

Bone Age Evaluation

- Left hand and wrist radiographs
- Results compared against standard
- Bone age calculated

- Constitutional delay of growth and puberty and endocrine disorders will have a delayed bone age
Case 4 Continued

You perform an initial evaluation of Ryan. His father is 177 cm (69 inches) tall and his mother is 164 cm (64 inches) tall. Ryan's growth velocity has been 5 cm per year for last 3 years. His physical exam is normal and he reports neither GI nor endocrine symptoms. His bone age is consistent with an 8-year old boy.
Short Stature Evaluation

Dysmorphic patient
- If proportionate growth
  - Consider genetic syndrome
  - Down syndrome, Turner syndrome
- If growth NOT proportionate
  - Evaluate for chondrodystrophy
Short Stature Evaluation

Growth velocity >= 5 cm / year
And delayed bone age
• Constitutional delay of growth and puberty

Child born AGA, falls to 3rd percentile during catch-down growth
Delayed onset of puberty which results in normal height

Short Stature Evaluation

Growth velocity >= 5 cm / year
And normal bone age
• Familial short stature
Projected height consistent with midparental height
• Idiopathic short stature
Short Stature Evaluation

Growth velocity < 5 cm / year
And delayed bone age
• Consider endocrine disorders

Weight tends to be normal or increased

Lab Evaluation

For an asymptomatic child with idiopathic short stature
• Full laboratory evaluation is expensive and low yield
• Two diseases most frequently identified
  • Celiac disease
  • Growth hormone axis problem

Lab Evaluation

If no etiology is suggested by history and physical:
• CBC
• CMP
• Bone Age
• ILGF-1
• IGFBP3

• Karyotype in girls


Short Stature – Differential Diagnosis

Normal variants
• Constitutional delay of growth and puberty
• Familial short stature
• Idiopathic short stature
Short Stature – Differential Diagnosis

Chronic disease
• Anemia
• Celiac disease
• Chronic renal insufficiency
• Inflammatory bowel disease

Endocrine Disorders
• Achondroplasia
• Acquired growth hormone deficiency
• Congenital growth hormone deficiency
• Congenital hypothyroidism
• Intrauterine growth deficiency
• Primary nutritional deficiency
Short Stature – Differential Diagnosis

Genetic conditions
• Turner syndrome

Referral to Pediatric Endocrinology

• IUGR who do not catch up by 2 years
• Height more than 3 SD below the mean (< 1st percentile)
• Growth velocity < 5 cm (2 inches) per year
• No onset of puberty by 14 years for boys and 13 years for girls
• Projected height more than 2 standard deviations (10 cm or 4 inches) below the midparental height
• Bone age more than 2 SD below chronological age
• Diagnosis for which growth hormone is indicated

Indications for Growth Hormone

• Idiopathic short stature
• Turner syndrome
• Chronic renal failure
• Prader-Willi syndrome
• Small for Gestational Age
• Noonan syndrome
• Short-stature homeobox-containing gene deficiency

Treatment: Growth Hormone

• Daily injections for several years
• Adverse events are rare
• Four years of treatment
  • Costs $100,000- $120,000
  • Results in average growth of 3.7 cm (1.46 inches)
Case 4 Continued

Ryan’s parents are both within normal adult height and Ryann’s mid-parental height is 50th percentile.
His growth velocity has consistently been 5 cm per year.
His bone age is delayed.
Basic labs are unremarkable.

Poll Question 5

What is Ryan’s most likely diagnosis?

A. Familial short stature
B. Idiopathic short stature
C. Celiac Disease
D. Constitutional delay of growth and puberty
Tall Stature

Defined as a height more than two standard deviations (greater than 97th percentile) above the mean for age

• Much less likely to be referred to pediatric endocrinology
• Intervention is usually not needed
Tall Stature - Differential

Normal variants
• Constitutional advancement of growth
• Familial tall stature

Endocrine disorders
• Hyperthyroidism
• Obesity
• Pituitary gigantism
• Precocious puberty

Genetic conditions
Disproportional overgrowth
• Beckwith-Wiedemann syndrome
• Homocystinuria
• Klinefelter syndrome (XXY)
• Marfan syndrome

Proportionate overgrowth
• Fragile X syndrome
• Sotos syndrome
• Weaver syndrome
Ryan is now 12 and his parents return to your office. They are concerned because his remains shorter than his school-aged peers and he has not started puberty. They again want to know if he should see a pediatric endocrinologist.
Poll Question 6

When should you consider the diagnosis of delayed puberty?

A. No signs of puberty at 2 SD above the mean
B. No signs of puberty at 13 years for girls
C. No signs of puberty at 14 years for boys
D. All of the above

Hormonal Changes in Puberty

1. Hypothalamus increases pulsatile secretion of gonadotropin releasing hormone (GnRH)
2. GnRH stimulate anterior pituitary to increase pulsatile secretion of gonadotropins: Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)
3. FSH and LH stimulate sex steroidogenesis
   • Estradiol in girls
   • Testosterone in boys
Disorders of Puberty

Precocious Puberty
• Onset of puberty at age 2-3 SD below mean
  • Before 8 years in girls
  • Before 9 years in boys

Delayed Puberty
• Absent signs of puberty at age 2-3 SD above mean
  • By 13 in girls
  • By 14 in boys

Puberty

1. Gonadarche – physical changes of puberty
   Triggered by GnRH
   • Girls – starts with breast development (mean age 10)
   • Boys – starts with testicular enlargement (mean age 11.5)

2. Adrenarche – development of axillary hair, body odor, mild acne
   Triggered by adrenal androgens
Disorders of Puberty Initial Workup

- FSH
- LH
- Testosterone (boys)
- Estradiol (girls)
- Bone age radiography

Additional testing is guided by history and physical

Delayed Puberty

Possible additional evaluation
(Guided by history of physical exam)
- TSH
- Prolactin
- ILGF-1
- Celiac disease
- Diabetes mellitus
- Karyotype
- Brain imaging
Delayed Puberty

Differential Diagnosis
• Constitutional delay of growth and puberty
• Hypergonadotropic hypogonadism
  (FSH and LH above prepubertal range)
• Hypogonadotropic hypogonadism
  (FSH and LH in prepubertal range)
  • Functional – chronic disease, stress or poor nutrition
  • Persistent – congenital abnormality of HPG axis or CNS pathology

Constitutional Delay of Growth and Puberty

Most common cause of puberty delay
• 70% boys
• 30% girls
• 75% of parents have a history of puberty delay
FSH and LH in prepubertal range
Hypogonadotropic hypogonadism

Functional
- Celiac disease
- Diabetes mellitus
- Hyperthyroidism
- Hypothyroidism
- Inadequate nutrition
- Inflammatory bowel disease

Hypogonadotropic hypogonadism

Persistent Genetic
- Congenital GnRH
- Kallmann syndrome

Persistent Acquired
- CNS trauma, surgery or radiation
- CNS tumors
Hypergonadotropic hypogonadism

- Chemotherapy, radiation or trauma to gonads
- Klinefelter syndrome (boys)
- Oophoritis or orchitis
- Turner syndrome (girls)

Treatment: Delayed Puberty

Jump-start therapy for constitutional delay of growth and puberty
- Boys > 14 years
  - Testosterone monthly injections
- Girls > 15 years
  - Estradiol overnight transdermal patch
Poll Question 7

Ryan’s growth and bone age are still consistent with his previous work up. He still has no gastrointestinal or endocrine symptoms. His FSH and LH are both in the prepubertal range. What is his most likely diagnosis?

A. Hypergonadotropic hypogonadism  
B. Constitutional delay of growth and puberty  
C. Functional hypogonadotropic hypogonadism  
D. Turner syndrome

Practice Recommendations

1. Measure weight and height over more than one visit. (LOE C)
2. Use World Health Organization growth charts for children up to 2 years of age and Centers for Disease Control growth charts for children to to 20 years of age. (LOE C)
3. Routine lab testing is rarely indicated for failure to thrive. Lab evaluation for short stature should be guided by the history and physical. (LOE C)
4. Boys without testicular growth by 14 years and girls without breast development by 13 years should be evaluated for delayed puberty.

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Questions
Additional Reading


Diabetes Treatment Update: After Metformin

Barbara Keber, MD, FAAFP
Mary Muscarello, MSN, ANP-C, CDE, CRRN

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Barbara Keber, MD, FAAFP

Physician, Northwell Health Physician Partners Family Medicine, Glen Cove, New York; Vice Chair/Associate Professor of Family Medicine, Department of Family Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; Chair of Family Medicine, Glen Cove Hospital, New York

Dr. Keber earned her medical degree from the State University of New York (SUNY) Downstate College of Medicine, Brooklyn, and completed her residency in family medicine at the Community Hospital of Glen Cove, New York. She has been a board-certified family physician for 35 years and currently works for Northwell Health Physician Partners Family Medicine at Glen Cove Hospital. For the past five years, the combined faculty and residency practice has had National Committee for Quality Assurance (NCQA) recognition as a Level 3 Patient-Centered Medical Home (PCMH), and Dr. Keber has been instrumental in developing the patient-centered approach and team-based care. In addition, she is the physician leader for the diabetes program in both the inpatient and ambulatory settings. She is currently the physician lead for the Enterprise Diabetes Project for the Northwell Health System, leading efforts to enhance and standardize diabetes care within the enterprise. She has lectured on topics related to diabetes care/management and team-based population health within the PCMH model of care.
Mary Muscarello, MSN, ANP-C, CDE, CRRN

Nurse Practitioner/Outpatient Diabetes Self-Management Program Coordinator/Inpatient Diabetes Educator,
Glen Cove Hospital, New York

Muscarello earned her Bachelor of Science (BS) degree in nursing from Molloy College in Rockville Centre, New York, and her master’s degree in adult health from Stony Brook University, New York. For more than 17 years, she has worked for Northwell Health in various positions, including acute rehab, and as a visiting nurse. A board-certified adult nurse practitioner and certified diabetes educator, she currently works in a hospital-based family medicine clinic, specializing in the care of patients who have diabetes. She works with a socioeconomically disadvantaged population, comprised mostly of immigrants from Central America who have limited English proficiency and limited financial resources. Because many of them have never attended school, literacy and numeracy are major challenges for Muscarello’s patients. She uses numerous hands-on tools to enhance her patients’ understanding of their condition and treatment. She believes that the marriage of evidence-based medicine, shared decision-making, and relationship-based care makes all the difference in successfully getting patients to goal. She has been nominated for and received several awards, including the Northwell Health President’s Award for Exceptional Patient/Customer Experience for the Eastern Region.

Learning Objectives

1. Evaluate current standards of care (screening, prevention, diagnosis, treatment, management) for patients with diabetes, or who are at risk for developing diabetes, for opportunities to update standards in accordance to current research and evidence-based guidelines.

2. Apply a patient-centered approach to incorporate guideline recommendations for intensifying therapy to achieve glycemic control.

3. Use medication which allow patients to achieve their individualized metabolic targets without weight gain or increasing their risk of developing treatment emergent hypoglycemia.

4. Encourage patients to remain adherent to their prescribed behavioral and pharmacologic therapeutic interventions.
Associated Sessions

• (PBL) Diabetes Treatment Update: After Metformin

Audience Engagement System

Step 1

Step 2

Step 3
Poll Question 1

Metformin has failed to get your patient to glycemic goal. How comfortable are you with intensifying therapy?

1. Very comfortable
2. Somewhat comfortable
3. Minimally comfortable
4. Not at all comfortable

THE STAGGERING COSTS OF DIABETES IN AMERICA

86 million Americans have prediabetes.

Nearly 30 million Americans have diabetes.

$1 in $3 Medicare dollars is spent caring for people with diabetes.

Diabetes and prediabetes cost America

$322 billion

$1 in $5 people care dollars is spent caring for people with diabetes.

Today, 3,835 Americans will be diagnosed with diabetes. Today, diabetes will cause:

- 260 Americans to undergo an amputation.
- $36 to enter end-stage kidney diseaseremark and
- 1,795 to develop severe retinopathy that can lead to vision loss and blindness.

Learn how to fight this costly disease at diabetes.org/congress

American Diabetes Association.
Goals of Care

• Reduce mortality
  – Cardiovascular disease (MI, CVA) is highest cause of mortality
• Enhance quality of life by reducing morbidity and other complications
  – Nephropathy, neuropathy, retinopathy, amputations other vascular complications
• Reduce patient burden

Goals of Treatment

• < 7% (ADA) for prevention of microvascular disease – level A
• < 6.5 % (ACCE) level D- but must be formulated in context of individual patient’s life expectancy, comorbid conditions
• < 8% for those elderly, chronic kidney disease, cognitive impairment, recurrent hypoglycemia, cardiovascular disease, those with short life expectancy
• Fasting glucose 80-130 mg/dl
• 2 hour PPG < 180 mg/dl
• Goals must be individualized
Evaluation of the Patient with Diabetes

- History
- Physical examination
- Labs
- Barriers to care

Patient Barriers

- Patient may be overwhelmed by new diagnosis
- Competing priorities
- Language barriers and/or limited literacy
- Issues with vision and dexterity
- Lack of perceived severity
- Limited financial resources and lack of transportation
- Cognitive impairment
- Depression and other mental health conditions
- Lack of diabetes education and training
Provider Barriers

• Time constraints
• Seemingly ever changing recommendations
• New medications continually coming on the market and patients requesting what they’ve seen on TV
• Lack of training on new medication devices
• Lack of educational support staff
• The dreaded “prior auth” for just about everything

It Takes a Team (ideal world)

• PCP-Physician/NP/PA
• Specialists-Endocrinology, Cardiology, vascular surgery, nephrology
• Podiatrist, Dentist
• CDE (Certified Diabetes Educator)
• Pharmacist
• Physical Therapist
• Registered Dietitian
• Social Worker, other behavioral health specialists
• Care Manager
• Nursing and clerical staff
Level B evidence
It Takes a Team (reality)

- PCP (Physician, NP, PA)
- Medical Assistant
- Clerical

Treatment

Lifestyle modification Always- don’t underestimate it!
- Diet with weight loss-5-10% weight loss can result in improved glucose control
- Exercise -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. Level A evidence
- Smoking Cessation
Poll Question 2

The goal for HbA1C is:

1. Always < 7%
2. < 7% for those with renal disease, frail elderly and those with cognitive impairment
3. < 9% for patients with cardiovascular disease
4. < 6.5% for those with recurrent hypoglycemia
5. Individualize treatment goals for the patient

While the A1C is important, it only gives you the 60 - 90 day average, not the whole story

<table>
<thead>
<tr>
<th>A1c %</th>
<th>Estimated Average Glucose mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>298</td>
</tr>
<tr>
<td>11.5</td>
<td>283</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
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<td>7.5</td>
<td>169</td>
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<tr>
<td>7 or less</td>
<td>154</td>
</tr>
<tr>
<td>6.5</td>
<td>140</td>
</tr>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>5.5</td>
<td>111</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
</tr>
</tbody>
</table>
Each of these patients has an A1C of 7%
So what does *average actually mean??*

<table>
<thead>
<tr>
<th></th>
<th>In-Range (70-180)</th>
<th>Hyper (&lt; 180)</th>
<th>Hypo (&lt; 70 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C 7%</td>
<td>100%</td>
<td>58%</td>
<td>18%</td>
</tr>
<tr>
<td>A1C 7%</td>
<td>24%</td>
<td>29%</td>
<td>9%</td>
</tr>
<tr>
<td>A1C 7%</td>
<td>24%</td>
<td>29%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Medications**

- Oral
- Injectable
There are many paths to get to goal

Which one right for your patient?

What Drives Choice of Medication?

• Insured vs uninsured
• Insurance coverage (deductibles / co-insurance)
• Risk vs benefit
• Side effect profile
• Secondary benefits (weight loss, ↓ BP)
• Patient willingness and ability to use
Uninsured Patients

Most cost effective medication:

• Metformin
• Sulfonylureas
• NPH and Regular insulin
• Mixed insulin

Don’t order expensive meds for uninsured patients

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

MONOTHERAPY*

Entry A1C < 7.5%
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGL
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

DUAL THERAPY*

Entry A1C ≥ 7.5%
- Met or other 1st-line agent
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGL
- SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

Entry A1C > 9.0%
- GLP-1 RA
- SGLT-2i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGL
- SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

SYMPTOMS

NO
DUAL Therapy
OR
TRIPLE Therapy
INSULIN or Other Agents
YES
ADD or INTENSIFY INSULIN

P R O G R E S S I O N O F D I S E A S E

ACCE 2017 from creative commons

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
Metformin First

- Inhibits glucagon release from liver and absorption of glucose by muscle
- First line- still for most patients-level A
- Lowers A1C by up to 2% points
- Then consider other options
- Low cost $, weight neutral
Metformin

- Common side effects: nausea, bloating, gas, diarrhea, metallic taste in mouth
- Better tolerated when dosing is titrated and taken with food, rather than empty stomach
- Work up to therapeutic dose of 1,000 mg BID
- Avoid TID dosing to reduce patient burden
- Extended release better tolerated but sometimes not covered by insurance. If not covered, encourage cash pay at big box store
- B12 deficiency (especially if use exceeds 10 yrs., anemia, neuropathy- level B)

Metformin Precautions/Contraindications

Avoid with Renal Dysfunction

Old recommendation: Avoid w/ SCr ≥1.5 in men and ≥1.4 in women

Newer Recommendation based on eGFR rather than SCr:
- eGFR > 45: no dose adjustment necessary; monitor renal function at least annually
- eGFR 30-45: use is not recommended for initiation of therapy; if eGFR falls to <45 mL/min/1.73m2 during therapy, consider benefits/risks of continuing therapy; can dose reduce by 50% and monitor renal function every 3 months
- eGFR <30: use is contraindicated

Glucagon-like Peptide-1 Receptor Agonists (GLP1 RA)

Injectable medication

- Increase in glucose-mediated insulin production by pancreatic β-cells - does not work if glucose level is normal
- Low incidence of hypoglycemia
- Slows gastric emptying
- Reduced glucagon secretion
- CNS actions- increased satiety → reduced intake
Benefits GLP-1 RA

- Weekly administration option an advantage
- Weight loss
- Reduction of A1C-1.28-1.48%
- Reduced cardiovascular events- level A
- Reduced kidney disease- level C

Side Effects/Precautions GLP-1 RA

Side Effects
- Nausea, vomiting-26%*
- Diarrhea- 6%*
- Pancreatitis (rare)
- Injection site reactions (rare)
- Medullary thyroid carcinoma (C cell)

*Usually self limited. Dose reduction can decrease incidence

Precautions
- Slow gastric emptying → altered absorption of oral medications
- Use with caution with medications with narrow therapeutic index or meds requiring rapid GI absorption
- Avoid in patients with gastroparesis
- Avoid with hx Medullary Thyroid carcinoma or pancreatitis
When to Choose

When metformin not tolerated or does not get patient to goal
• Insured patients only
• Need for weight loss
• Second line agent after metformin
• High cardiovascular risk- diagnosed ASCVD
• Insurance dictates which GLP1 used

GLP1 Choices

• Liraglutide (Vicotoza) taken daily
• Lixisenatide (Adlyxin) take daily
• Exenatide (Byetta) taken twice daily
• Exenatide extended release (Bydureon) taken weekly
• Dulaglutide (Trulicity) taken weekly
• Semaglutide (Ozempic) taken weekly
Patient Education

• Must receive education on pen use and injection technique as each GLP1 has a different mechanism
• Medication storage
• GI effects usually decrease after 1st week
• Injection site reactions rare but can happen
• Report side effects

Poll Question 3

The following are all good candidates for GLP1 RA therapy EXCEPT:

1. Obese 53 yr old, HTN, A1C 7.6% on Metformin
2. Obese 36 yr old, HTN, A1C 11%, uninsured, history of pancreatitis
3. Obese 45 yr old, can’t tolerate Metformin, A1C 8%
4. 72 yr old, A1C 9%, on Lantus, e-GFR 65 ml/min
Cardiovascular Benefits for GLP1 RA

• Several studies (LEADER trial –liraglutide, SUSTAIN-6- semaglutide, ELIXA trial- lixisenatide) have shown reduced risk for MI, CVA and CV mortality and have been given additional FDA approval for this use.
• Level A use

SGLT-2 Inhibitors
(Sodium–Glucose Cotransporter 2 Inhibitors)

Mechanism of Action

• SGLT2 is situated at the first two convoluted segments of the proximal tubule
• Reabsorbs ~90% of the filtered glucose
• Enhance urinary excretion of glucose and decreases reabsorption → lowering the glucose in the blood stream
Poll Question 4
The following are benefits of the use of SGLT2 Inhibitors:

1. Reduced hospital admissions for congestive heart failure
2. Reduced diabetic nephropathy
3. Reduce Triglycerides
4. Reduction in BP
5. All of the above
Benefits of SGLT2 Inhibitors

- Oral medication
- Can be taken anytime
- Lowers A1C 1-2%
- No hypoglycemia
- ↓ BP
- ↓ weight
- ↓ MACE, HF, CKD with some agents

SGLT2 Inhibitors

**Side Effects**
- Polyuria → dehydration
- Hypotension, dizziness
- ↑ UTI and genital infections
- ↑ risk for DKA (rare)

**Considerations**
- Needs renal dose adjustment
- Expensive
- ↑ LDL-C and creatinine (transient)
- ↑ risk for amputation and fractures (canagliflozin)
SGLT2 Choices

- danagliflozin (Invokana)
- dapagliflozin (farxiga)
- empagliflozin (Jardiance)
- ertugliflozin (Steglatro)
- Many available as combination with metformin, DPP4 inhibitors

Effects of SGLT2 Inhibitors on Congestive Heart Failure

- Reduced hospitalizations for heart failure (both preserved ejection fraction and reduced ejection fraction) for 3 different SGLT2 inhibitors in 3 large studies-CANVAS, DECLARE-TIMI, CREDENCE)
- Reduced CV mortality –level A
- Level C use for nephropathy
More SGLT2 Inhibitors to Come

• May also improve the development of non-alcoholic steatohepatosis (NASH) or development to cirrhosis

• Trials currently ongoing to assess the through reductions in intra-glomerular pressure, SGLT2is attenuate albuminuria by 30-40%

Patient Education

• Advise about hygiene to reduce incidence of genital infections and UTIs
• Educate about the lowering of BP which may cause lightheadedness and to rise from lying or sitting positions slowly
• Advise of increased urination at onset of therapy which will decrease over time-need for active hydration
Sulfonylureas

**MOA:** Closes K+ ATP channels on the beta cell plasma membranes
Increases insulin secretion from beta cells

**Benefits**
- Oral medication
- Easy to administer
- Low cost$
- HbA1c reduction: 1.5%

**Side effects and considerations**
- High risk for **hypoglycemia**, especially if poor or irregular PO intake, elderly
- Long half-life, effects can last up to 72 hours
- Weight gain
- Requires renal adjustment
- Increased cardiovascular risk

DDP-4 Inhibitors

**Mechanism of Action**
- Prevents the degradation of native GLP-1
- ↑ insulin secretion
- ↓ glucagon secretion
- Is glucose dependent
**DPP-4 Inhibitors**

**Benefits**
- HbA1c reduction: 0.5–0.8%
- Weight Neutral
- Glucose dependent- no hypoglycemia
- Well tolerated, oral, once daily

**Side effects and considerations**
- High cost $$$
- ↑ HF hospitalization
- Urticaria /angioedema (rare)
- Dose adjustment/avoidance for renal disease
- Potential increase risk for pancreatitis, arthralgia, URI, and bullous pemphigoid

---

**DPP-4 Inhibitors -Choices**

- Januvia (Sitagliptin)
- Galvus (Vildagliptin)
- Onglyza (Saxagliptin)
- Tradjenta (Linagliptin)

**NOT TO BE USED IN ADDITION TO GLP1 RA**
Poll Question 5

Insulin is appropriate for all the following patients except:

1. Newly diagnosed patient with HbA1C of greater than 10% with symptoms
2. HbA1C less than 7% in patient with Type 2 diabetes
3. A morbidly obese patient treated with 3 medications and still not at goal HbA1C
4. Type 2 DM with e-GFR 20 ml/min, A1C 9%
When to Start Insulin

- Newly diagnosed, symptomatic with A1C > 10%
- Not at goal when using 3 non-insulin agents
- Uninsured, not at goal using Metformin and sulfonylurea
- Patients with renal disease that cannot tolerate other agents

Utilize Your Resources

Majority of pharmaceutical companies very willing to help
- Medical liaisons
- Certified Diabetes Educators
- Willing to come to your office
- “Train the trainer”
- Provide non-branded educational materials
Optimization of Treatment-Avoiding Clinical Inertia

- Use a patient centered approach with a team of healthcare professionals to engage the patient in caring for themselves and their diabetes
- Avoidance of medications which increase complications of hypoglycemia, weight gain, worsen renal disease or cardiac disease
- **Choose according to comorbid conditions:**
  - Obesity, Coronary artery disease- GLP1 RA
  - Heart failure, renal disease, hypertension- SGLT2 inhibitor

Practice Recommendations

- Reinforce lifestyle changes and smoking cessation at EVERY visit
- Let patients know which meds will continue and which will be discontinued
- Work with what’s covered by insurance
- Use coupons and big box store pharmacies
- Discuss options with patient and allow for shared decision making
- Provide education on use of medication pens
- Educate on side effects and importance of notifying provider, not just stopping medication
- Praise ALL progress. Diabetes is a lot of work!!
- Always offer hope
Contact Information

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Questions
References

1. Diabetes Care January 2019 Volume 42, Supplement 1 American Diabetes Association Standards of Care 2019, on line version updated as of June 2019 https://doi.org/10.2337/dc19-Sint01

2. ACCE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2019 January 2019


References Cont’d.


7. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2019, American Diabetes Association, Diabetes Care 2018 Jan; 42(Supplement 1): S73-S85.

Endocrine Disorders in Pregnancy

David Glenn Weismiller, MD, ScM, FAAFP

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Dr. Weismiller is a graduate of Jefferson Medical College of Thomas Jefferson University in Philadelphia, Pennsylvania, and completed his residency at the University of Virginia Health Sciences Center in Charlottesville. Subsequently, he completed a fellowship in maternal-child health and earned a graduate degree in epidemiology at Brown University School of Medicine, Providence. A professor of family medicine at the new medical school of the University of Nevada, Las Vegas, he provides full-scope care that includes inpatient and maternity care. A proponent of “reflection in practice” and “learner-centered instruction,” he is recognized nationally for his work in continuing medical education and faculty development.

Having taught board review programs for the AAFP for more than 20 years, Dr. Weismiller is the founding and current chair of the AAFP Family Medicine Board Review Express™, as well as the AAFP’s annual Family Medicine Update live course. He is a frequent presenter at AAFP Family Medicine Experience (FMX) and teaches American Board of Family Medicine (ABFM) Knowledge Self-Assessments throughout the country. He is the author of numerous publications on issues related to women’s and children’s health, and he is an advocate for empowering individuals to make sound health care choices.
Learning Objectives

1. Develop screening protocols to identify patients at risk for developing pregnancy-related endocrine disorders.

2. Order appropriate laboratory or radiologic tests to confirm diagnosis us suspected endocrine disorders.

3. Recognized indication for referral and possible admission, coordinating care and follow-up as necessary.

4. Develop collaborative care plans that foster patient adherence to prescribed lifestyle modifications and pharmacotherapy.

Audience Engagement System
Diabetes mellitus

Affects 7% of pregnancies

Fetus of a diabetic woman in excellent glucose control

Fetus of a diabetic woman in poor glucose control
Diabetes mellitus

**Pregestational**
- 10% of pregnancies complicated by DM
  - Major congenital malformations remain the leading cause of mortality and serious morbidity in infants of mothers with type 1 and type 2 diabetes
  - Because few well-designed studies have been performed, many of the guidelines are based on expert and consensus opinion

**Gestational**
- 90% of pregnancies complicated by DM
  - > 50% eventually develop type 2 DM

AES Question #1

Prepregnancy counseling for women with pregestational diabetes mellitus has been reported to be beneficial and cost effective and should be encouraged. *(Level B evidence)*

Which one of the following targets is recommended as the optimal HbA$_{1c}$ entering pregnancy?

A. $\leq 5.7$
B. $\leq 6$
C. $\leq 6.5$
D. $\leq 7$
Pregestational Diabetes
Prepregnancy visit

- Counsel – potential complications in pregnancy
  - Fetal anomalies
    - most common cause of neonatal death in children of mothers known to have DM before pregnancy is congenital anomalies
  - PTD
  - Preeclampsia
    - 15-20% of pregnancies
  - Fetal macrosomia
    - Shoulder dystocia - >2x
  - Mode of delivery
  - Hyperglycemia
  - Worsening diabetic retinopathy and nephropathy
  - Neonatal complications

- Evaluate for baseline complications: hypertension, nephropathy, retinopathy, CVD
- Ensure adequate contraception if NOT planning pregnancy immediately (LARC preferred)
- Plan to optimize HbA1c (< 6% - anomaly rate 2-3%)
  - HbA1c near 10% - anomaly rate 20-25%
- Discuss plan to increase folic acid when attempting to get pregnant (800 ug to 1 mg)

Pregestational DM
Neonatal Consequences

- Poorly controlled Pregestational DM
  - Profound hypoglycemia
  - Increased rate of RDS
  - Polycythemia
  - Organomegaly
  - Electrolyte disturbances
  - Hyperbilirubinemia
  - Long-term outcomes
    - Obesity
    - CHO intolerance
Pregestational Diabetes

First trimester

• Prenatal labs/tests include HgbA$_1c$, TSH, 24-hour urine (if no baseline), EKG
• Evaluation
  • Ophthalmologist
  • Dietician
    • dietary approach to glycemic control is focused on careful carbohydrate counting and allocation of appropriate ratios of carbohydrates to meals and snacks (Level B)
• Possibly endocrinologist, cardiologist, nephrologist

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Pregestational Diabetes

Second trimester

• Start low-dose aspirin 12-28 weeks of gestation – optimally 16 weeks EGA (Level B)
  • high-risk factor for the development of preeclampsia
• US including a detailed anatomical survey
• Consider fetal echocardiography

Level B—Recommendations are based on limited or inconsistent scientific evidence.
Pregestational Diabetes

Third trimester

- Evaluate fetal growth
- Start low-dose aspirin by 28 weeks of gestation if NOT started in the second trimester
- Fetal monitoring (nonstress test, MBPP, BPP)
  - usually once or twice per week (Level B)

Level B—Recommendations are based on limited or inconsistent scientific evidence.

---

Pregestational Diabetes

- Treatment (Level B)
  - Use of all oral hypoglycemic agents for control of pregestational type 2 diabetes mellitus during pregnancy should be limited and individualized until data regarding the safety and efficacy of these drugs become available
  - Insulin is the preferred treatment for pregestational diabetes in pregnancy not controlled by diet and exercise

Level B—Recommendations are based on limited or inconsistent scientific evidence.
**Pregestational Diabetes**

**Delivery**

- If EFW ≥ 4500 g, consider cesarean delivery *(Level C)*
- Without vascular complications and well controlled blood glucose levels, deliver at 39 0/7 weeks to 39 6/7 weeks EGA
- In women with vascular complications or poorly controlled blood glucose, consider delivery at 36 weeks 0/7 weeks to 38 6/7 weeks EGA, and in rare cases, even earlier

AES Question #2

Gestational diabetes has been associated with each of the following perinatal complications EXCEPT:

A. Increased frequency of maternal hypertensive disorders
B. Increased risk of operative delivery
C. Increased frequency of neonatal hyperglycemia
D. Increased risk of intrauterine fetal death during last 4-8 weeks of gestation
Gestational Diabetes

- Condition is increasing as obesity and older age at pregnancy become more common
- Increased risk:
  - Gestational hypertension
  - Preeclampsia
  - Cesarean delivery
  - 7-fold increased risk of developing diabetes later in life

Why All the Fuss …

Adverse Outcomes

Maternal
- Increased frequency
  - Maternal hypertensive disorders
  - Cesarean delivery
- Increased risk of intrauterine fetal death during last 4-8 weeks of gestation
  - Fasting hyperglycemia (> 105 mg/dL)

Fetal
- Excessive fetal growth (macrosomia)
  - Increased risk for operative delivery
  - Shoulder dystocia
  - Birth trauma
- Neonatal morbidity
  - Hypoglycemia
  - Hypocalcemia
  - Hyperbilirubinemia
  - Polycythemia
Detection of GDM

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
</table>
| ACOG (2018)  | • Use a 2-step method at 24-28 weeks (Level B).  
• Screen for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors | Use a blood glucose level of either 135 or 140 mg/dL with factors such as community prevalence rates of GD determining the cutoff. |
| USPSTF (2014) | • Screen asymptomatic women after 24 weeks (Grade B).  
• Current evidence is insufficient to assess the balance of benefits and harms of screening for GD in asymptomatic pregnant women before 24 weeks of gestation (Grade I). | Goal was not to look at the performance or whether one method was better than another for screening. Found treating can significantly reduce the risk of preeclampsia, macrosomia, shoulder dystocia. |
| ADA (2014)   | • Screen for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors  
• Screen at 24-28 weeks if not previously known to have diabetes. | Updated Guidelines: Use either:  
1. 1-step method (75g OGTT)  
2. 2-step method |

RISK FACTORS (Screen early)…ACOG, NIDDK,ADA

- Patient is overweight with BMI of 25 (23 in Asian Americans), and ONE or more of the following:
  - Physical inactivity
  - First-degree relative with diabetes
  - Known impaired glucose metabolism
  - Previous pregnancy history of
    - GDM
    - Macrosomia (>4000 g)
    - Stillbirth
  - Hypertension (>140/90 or being treated)
  - HDL cholesterol < 35 mg/dL
  - Fasting TG ≥ 250
  - PCOS, acanthosis nigricans, nonalcoholic steatohepatitis, morbid obesity and OTHER conditions associated with insulin resistance
  - HgbA1c>5.7%, impaired glucose tolerance or impaired fasting glucose on previous testing
  - ASCVD
  - High risk ethnicity

Two-Step Approach in USA  
ACOG 2018, ADA 2014

- 24-28 weeks (routine)
- Initial screening: 50 g oral glucose load (glucose challenge test)
  - > 135 or > 140 mg/dL* ⇒ 3-hour OGTT
  - Note: > 190, > 90% abnormal 3-hour
- 3-hour OGTT ± ⇒ 2 or more abnormal values = (+) GDM
  - Overnight fast, 100 g glucose polymer
  - Abnormal plasma blood glucose: > fasting 95 mg/dL, 1h 180, 2h 155, 3h 140

*Either threshold acceptable, ACOG 2018 (Level C).
* Can also be used as a 1-step method for high-risk women or in areas in which the prevalence of insulin resistance is 5% or higher (eg, southwestern and southeastern US).

One abnormal value on 3-hour OGTT?

- One abnormal value - significantly increased risk of adverse perinatal outcomes compared with women without GDM.
- Although a higher level of scrutiny may be focused on this subset of women, further research is needed to clarify the risk of adverse outcomes in patients with one abnormal value on the 100-g, 3-hour OGTT and whether they would benefit from treatment.

Cheng YW, Block-Kurbisch I, Caughey AB. Carpenter-Coustan criteria compared with the national diabetes data group thresholds for gestational diabetes mellitus. Obstet Gynecol 2009;114:326–32.
Gestational Diabetes Mellitus Treatment
ACOG 2018

- Initial management (Level A)
  - Nutritional counseling by registered dietician
  - Advice on moderate exercise program (if possible); minimum of 150 minutes per week
- No conclusive evidence for the threshold value at which clinicians should start pharmacologic therapy
- Pharmacologic treatment
  - Insulin is considered **PREFERRED** treatment in pregnancy (Level A)
  - Glyburide treatment should **NOT** be recommended as a first-**CHOICE** pharmacologic treatment because, in most studies, it **DOES NOT** yield equivalent outcomes to insulin (worse outcome including macrosomia and birth injury (Level B)
  - In women who decline insulin therapy or if unable to safely administer, metformin is a reasonable second-line choice (Level B)


Gestational Diabetes Mellitus
*Maternal Surveillance – Glucose Monitoring*

- **Glucose Target Levels**
  - Fasting or preprandial < 95 mg/dL
  - 2-hour postprandial BG < 120 mg/dL (1 hour < 140mg/dL)
  - 1-2 times per week versus daily; review weekly
- **Pharmacologic Treatment (if on more than 3 occasions)**
  - > 95 mg/dL fasting whole blood glucose or
  - ≥ 120 mg/dL 2 h postprandial
  - Daily glucose monitoring
Gestational Diabetes Mellitus
Fetal Surveillance/Assessment (Level C)

- **Third trimester**
  - Increased risk for fetal demise
    - Preexisting DM
    - Fasting glucose >105 mg/dL
  - Delay delivery safely in order for the fetus to mature
  - Abnormal results are rare when diabetes well-controlled, no vascular disease or hypertension

- **Antenatal Testing**
  - Modified Biophysical Profile (MBPP)
    - NST and AFI
  - Biophysical Profile (BPP)
  - Contraction Stress Test (CST)

- **Ultrasound**
  - Amniotic Fluid Index (AFI)
  - Asymmetric fetal growth
  - Estimated fetal weight (EFW)

Gestational Diabetes Mellitus
Fetal Surveillance/Antepartum

- **Well-controlled A₁ GDM (Level C)**
  - no consensus regarding criteria for initiation and frequency (MBPP, BPP)
    - beginning 34-40 weeks versus none
  - More intensive biophysical testing
    - beginning at 32-34 weeks, twice weekly?
      - insulin requirement (A₂, B)
      - hypertension
      - previous stillbirth or other adverse obstetrical history
Gestational Diabetes Mellitus

Fetal Surveillance/Ultrasound

- Assessment for asymmetric fetal growth (early third trimester) may aid in identifying fetuses that can benefit from maternal insulin therapy
- Aid in the timing and route of delivery?
  - Estimate fetal size
    - CPD and birth trauma increase after 4000g
  - \( \geq 4500 \text{ g} \) - C-section may be best option (Level C; previously Level B)*
    - May reduce likelihood of permanent brachial plexus injury in the infant
  - 4000 to 4500 g – consider:
    - Past delivery history
    - Clinical pelvimetry
    - Progress of labor


Gestational Diabetes Mellitus

Timing of Delivery?

- Timing of delivery in women with GDM that is controlled with only diet and exercise (A1GDM) should NOT be before 39 weeks gestation, unless otherwise indicated. Expectant management up to 40 6/7 weeks of gestation in the setting of indicated antepartum testing is generally appropriate (Level C)
- GDM well controlled on medications (A2GDM) or Type 2, delivery is recommended at 39 0/7 to 39 6/7 weeks of gestation (Level C)

ACOG – 2018
Gestational Diabetes Mellitus

**Timing of Delivery?**

- **Poorly controlled** – Expert guidance supports earlier delivery but data lacking regarding precise timing
  - Delivery between 37 weeks 0 days and 38 weeks 6 days may be justified
  - Delivery between 34 weeks 0 days and 36 weeks 6 days reserved for (1) failure of in-hospital glycemic control or (2) abnormal fetal testing
- Council regarding risks/benefits of **scheduled cesarean delivery** when EFW > 4500 g (Level C)

---

**Long-Term Considerations**

- Increased risk for recurrence of GD
  - 33%-50% likelihood
- Increased risk for development of diabetes after pregnancy
  - Up to 1/3 will have diabetes or impaired glucose metabolism at postpartum screening
  - 35% of women 5-10 years after parturition
- Offspring – increased risk
  - Obesity
  - Glucose intolerance
  - Diabetes in late adolescence and young adulthood
Postpartum

- Reclassification of maternal glycemic status at least 4 weeks after delivery (preferred 4-12 weeks, ACOG 2018) [Level C]
  - FPG or 2-hr OGTT
- Reassessment of glycemia every one (USPSTF) to three years (ADA) [SOR:C], if above normal; yearly assessment (ADA) if impaired fasting glucose or impaired glucose tolerance at 6-12 weeks

Management of Postpartum Screening Results

**Gestational diabetes**

- FPG or 75-g, 2-hr OGTT at 4-12 weeks postpartum
  - FPG > 125 mg/dL or 2-hr glucose > 199 mg/dL
    - Diabetes mellitus
    - Refer for diabetes management
  - FPG 100-125 mg/dL or 2-hr glucose 140-199 mg/dL
    - Impaired fasting glucose or IGT or both
    - Consider referral for management
    - Weight loss and physical activity counseling as needed
    - Consider metformin if combined impaired fasting glucose and IGT
    - Medical nutrition therapy
    - Yearly assessment of glycemic status
  - FPG < 100 mg/dL or 2-hr glucose <140 mg/dL
    - Normal
    - Assess glycemic status every 1-3 years
    - Weight loss and physical activity counseling as needed
Best Practice Recommendations

- Nutritional Counseling
  - Insulin is the preferred pharmacologic therapy
    - Human preferable
    - Insulin analogs have not been adequately tested
  - Oral agents have not been generally recommended
  - Glucose monitoring

- Programs of moderate physical activity have been shown to lower maternal glucose concentrations
  - Impact on neonatal complications awaits rigorous clinical trials

- Delivery during the 38th week is recommended
Thyroid Disorders

- Fetus dependent on maternal thyroxine (T4) in early pregnancy.
- Maternal thyroid gland is required to increase thyroid hormone synthesis by up to 50% to meet the increased demands of pregnancy due to placental transfer of T4, increased thyroid hormone metabolism, increased renal iodine losses and changes in levels of T4 binding proteins. These changes also affect laboratory thyroid function test assays.
- Thyroid stimulating hormone (TSH) is the most reliable measure of thyroid function during pregnancy. Pregnancy- and trimester-specific laboratory reference ranges should be used if available.
Regulation of Thyroid Function

1. TRH from hypothalamus stimulates anterior pituitary to release TSH
2. Release of TSH stimulates all thyroid function
3. T3 and T4 release increases basal metabolic rate
4. Negative feedback loop: T3 and T4 act on hypothalamus and pituitary to suppress further TRH and TSH release

Changes in Thyroid Function Test Results in Normal Pregnancy and in Thyroid Disease

<table>
<thead>
<tr>
<th>Maternal Status</th>
<th>TSH</th>
<th>Free T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Varies by trimester*</td>
<td>Raised to no change</td>
</tr>
<tr>
<td>Overt Hyperthyroidism</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>Decrease</td>
<td>No change</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>Increase</td>
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</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>Increase</td>
<td>No change</td>
</tr>
</tbody>
</table>

*The level of TSH decreases in early pregnancy because of weak TSH receptor stimulation due to substantial quantities of human chorionic gonadotropin during the first 12 weeks of gestation. After the first trimester, TSH levels return to baseline values.
**Physiological changes in pregnancy and their impact on the thyroid**

- **Increase in circulating hCG stimulating TSH receptors**
  - Raised free T4, suppression of TSH
- **Increase in hepatic production of TBG**
  - Raised Total T4
- **Increased urinary iodine excretion**
  - Higher iodine requirement; goiter and hypothyroidism in iodine deficient areas
- **Activation of placental deiodinase type 3 enzyme**
  - Peripheral degradation of T4 and T3; demand for increased thyroid hormone production
- **Increased Plasma volume**
  - Increase in T4 and T3 pool
- **Immunological changes**
  - Decreased thyroid Ab titers; improvement in Graves’ disease

**Thyroid Gland and Pregnancy**

- Glandular hyperplasia and increased vascularity result in moderate thyroid enlargement but not thyromegaly
  - Thyroid function tests are NOT indicated in asymptomatic pregnant women with slightly enlarged thyroid glands (Level B)
  - Maternal thyroid volume is 30% larger in the third trimester than in the first
- Any goiter or nodule recognized during pregnancy should be considered pathologic
Thyroid function and the Fetus

- Maternal T4 is transferred to the fetus throughout the entire pregnancy and is important for normal fetal brain development
  - The high placental content of D3 inactivates most maternal T3 and T4, and very little free hormone reaches fetal circulation
- It is especially important before the fetal thyroid gland begins concentrating iodine and synthesizing pituitary TSH and thyroid hormone at approximately 12 weeks of gestation
- After 15-18 weeks, the fetus controls most of its own thyoidal secretion

Whom to screen in early pregnancy for thyroid dysfunction

- No evidence for universal screening
- Women at high risk – TSH BEFORE conception and as soon as pregnancy is confirmed.
  - TSH > 2.5 IU/L – obtain FT4 and Thyroid peroxidase antibody (TPOAb)

**High Risk**
- History of previous thyroid dysfunction
- Current symptoms suggestive of hyper- or hypothyroidism
- Known (+) thyroid antibodies
- Age ≥ 30 years
- Any history of autoimmune disease
- History of previous pregnancy loss, preterm delivery, or infertility
- Use of lithium, amiodarone or recent iodinated contrast use
- History of head and neck radiation
- Molar pregnancy
- Goiter
An approach to the management of abnormal TSH levels in pregnancy

Pregnant women at high risk for thyroid dysfunction

*Strong recommendation, moderate-to-high-quality evidence

Measure TSH levels in early pregnancy. If > 2.5 mIU/L measure T4 levels

![Flowchart diagram]

AES Question #3

In considering a pregnant patient with hyperthyroidism, which one of the following statements is true?

A. Serum Free T4 will be decreased
B. Inadequately treated, it is associated with a greater risk of preterm delivery
C. Toxic nodular goiter is the most common cause
D. It often improves in the second and third trimester due to the immunosuppressive effects of pregnancy
Hyperthyroidism

**Etiology**
- Graves’ Disease (30-80 per 100,000 person-years) – accounts for 95% of cases
- Toxic nodular goiter (1-2 per 100,000 person-years)

✓ Often improves in the second and third trimester due to the immunosuppressive effects of pregnancy

**Signs and Symptoms are similar to the nonpregnant state**
- Problem is that some symptoms of hyperthyroidism are similar to symptoms of pregnancy
- Serum TFTs differentiate thyroid disease from nonthyroid disease

**Best treated prior to pregnancy**

**Goal of Treatment:**
- Control thyrotoxicosis while avoiding fetal or neonatal transient hypothyroidism

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Hyperthyroidism

**Diagnosis**

**Clinical suspicion**
- Infertility
- Hyperemesis gravidarum
- Failure of nonobese women to gain weight
- Classic Signs of Graves Disease

**Highly sensitive third generation tests**
- TSH (Low)
- Free T4 or FTI (Increased)
  - Monitored to manage thyroid disease in pregnancy
# Thyroid Disease

## Effects of Pregnancy and Hyperthyroidism on Tests commonly used to evaluate Thyroid Function

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<thead>
<tr>
<th>Test</th>
<th>Normal Pregnancy</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>No change</td>
<td>Decreased</td>
</tr>
<tr>
<td>TBG</td>
<td>Increased</td>
<td>No change</td>
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<tr>
<td>Total T4</td>
<td>Increased</td>
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<tr>
<td>Free T4</td>
<td>No change</td>
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<tr>
<td>FTI</td>
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<td>Total T3</td>
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- Most of the pregnancy-induced changes in thyroid physiology are stimulated by hyperestrogenemia which in turn causes production of altered TBG.
- Changes in structure and function of the gland during pregnancy can mimic some of the effects of hyperthyroidism

## Transient gestational hyperthyroidism

- Common cause of mild hyperthyroidism secondary to thyroid stimulation by beta human chorionic gonadotrophin
- Generally limited to the first half of pregnancy
- Seen more often in women with hyperemesis and those with high beta human chorionic gonadotrophin levels due to molar pregnancy or multiple gestation
- Antithyroid medications are NOT indicated for women with gestational hyperthyroidism
**Thyrotoxicosis Management**

- Controlled medically, does not pose a serious threat to the mother
  - Use the least amount of medication required to achieve clinical euthyroidism *(Level B)*
    - may take 3-4 weeks to be reflected in labs
  - Aim of treatment with antithyroid medications - maintain a free T4 level at the upper end (or within 10%) of the nonpregnant reference range
- Mechanisms:
  - directed at blocking thyroid hormone production
    - e.g., thioureas
  - directed at peripheral manifestations of disease
    - e.g., beta blockers

**Maternal thyrotoxicosis**

- Inadequately treated – associated with a greater risk:
  - Preterm delivery
    - Including medically indicated preterm deliveries
  - Severe preeclampsia
  - Heart failure
  - Miscarriage – (no data to support this claim)
  - Fetal
    - LBW
### Hyperthyroidism

#### Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Monitoring</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylthiouracil (PTU)</td>
<td>Start 100-150 mg q 8 hours (300-450 mg/day)</td>
<td>✓ Increase to control thyrotoxicosis</td>
<td>✓ May require doses of 600-900 mg per day</td>
</tr>
<tr>
<td>Methimazole</td>
<td>– Second and third trimesters (if needed, when risk of malformation lower, preferred due to lower risk of hepatotoxicity)</td>
<td></td>
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</tr>
<tr>
<td>Beta blockers</td>
<td>may be used for rapid control of adrenergic symptoms</td>
<td></td>
<td></td>
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- The birth defects associated with propylthiouracil are generally milder and more easily corrected so it is used preferentially before a planned pregnancy and during the first trimester.

#### Effects on Fetus and Infant

- Thioureas cross the placenta
  - can cause fetal hypothyroidism and goiter
  - appear to have no subsequent growth and development adverse effects

- Morbidity and mortality - infants born to women:
  - who remain thyrotoxic despite therapy
  - who do not receive adequate prenatal care/treatment

- Fetal Thyrotoxicosis
  - in about 1% of mothers with Graves’ disease
  - Consider in all women with a history of Graves’ disease
  - If diagnosed – consultation with a clinician with expertise in such conditions warranted
History of Graves’ Disease
*Treated with surgery or radioactive iodine*

- TRAb levels measured in early pregnancy – if (+), repeat at 18-22 weeks’ gestation
  - Can cross placenta cause fetal hyperthyroidism and neonatal Graves’ disease
- Women with active Graves’ disease or (+) TRAb at 18-22 weeks – monitoring for fetal hyperthyroidism (MFM specialist)
- TRAb level is elevated at 18 to 22 weeks’ gestation or in women with active Graves’ disease on treatment, measurement of TRAb levels at 30 to 34 weeks’ gestation can guide decisions about neonatal and postnatal monitoring

Hypothyroidism in Pregnancy

- Difficult to diagnose
  - Subclinical disease (elevated TSH with normal free T4) more common than overt disease
    - Subfertility
    - Poor pregnancy outcomes: increased risk of SpAB, PTD, preeclampsia, GDM, IUGR, PROM
- Untreated hypothyroidism
  - Low-birth-weight infants
    - Medically indicated preterm delivery, preeclampsia, placental abruption
    - ? IUGR (not clear if independent of other complications)
  - Pregnancy loss
  - Impaired fetal neurocognitive development
- Hashimoto’s thyroiditis is the most common cause of hypothyroidism in pregnancy
Hypothyroidism

Diagnosis

• Rise in the level of circulating T4 expected during pregnancy fails to take place (low free T4) and level of TSH is elevated OR
• TSH > 10 mIU/L regardless of free T4 level
• NOTE: There is insufficient data to warrant routine screening of asymptomatic pregnant women for hypothyroidism (Level C)

Thyroid Disease

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• Most of the pregnancy-induced changes in thyroid physiology are stimulated by hyperestrogenemia which in turn causes production of altered TBG
• Changes in structure and function of the gland during pregnancy can mimic some of the effects of hyperthyroidism
Using TPOAb

- Women who are (+) TPOAb – increased rates if miscarriage and PTD – independent of thyroid function
- Thus, measurement recommended to assist with decision making on when to treat subclinical hypothyroidism
- High-quality randomized clinical trials on levothyroxine replacement to treat subclinical hypothyroidism during pregnancy are limited

Levothyroxine in pregnancy – data is mixed

| Trial                                                                                                                  | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Limitations                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Controlled Antenatal Thyroid Screening (CATS)-I and CATS-II trials                                                   | No significant difference in intelligence quotient in children aged 3 and 9.5 years of mothers with subclinical hypothyroidism randomized to levothyroxine treatment or placebo                                                                                                                                                                                                                                                                                                                                                      | Late commencement of levothyroxine at 13 weeks of gestation                                                                                     |
| Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy                                           | No improvement in cognitive outcomes in children of mothers treated for subclinical hypothyroidism at 5 years of age                                                                                                                                                                                                                                                                                                                                                                           | Late commencement of levothyroxine at 17 to 18 weeks of gestation                                                                                     |
| Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease           | Levothyroxine replacement may reduce the rates of preterm delivery in women with subclinical hypothyroidism and positive TPOAb                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                      |
Hypothyroidism detected in early pregnancy

**Treatment**

- TSH > 10mIU/L
  - Begin full dose* replacement

<table>
<thead>
<tr>
<th>TSH Level (mIU/L)</th>
<th>Initial dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limit of normal to 5</td>
<td>1 to 1.5 mcg/kg daily (range 50 to 75 mcg daily)</td>
</tr>
<tr>
<td>5-10</td>
<td>1 to 1.7 mcg/kg daily (range 75 to 100 mcg daily)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1.7 to 2.5 mcg/kg daily (range 100 to 200 mcg daily) and consider referral to endocrinologist</td>
</tr>
</tbody>
</table>

* Based on lean bodyweight

- Goal is to maintain the TSH in the low normal range
- Monitor TSH every 4-6 weeks until stable then every 8 weeks with a final check at 28-32 weeks
- Thyroxine requirement usually increases as the pregnancy advances
- Fetal surveillance????
- Following delivery, dose of levothyroxine can be halved, or ceased if on 50mcg daily or less during pregnancy, and thyroid function checked two to three months’ postpartum
Treatment of pre-existing hypothyroidism

• Levothyroxine dose increase
  • 20-30% increase when pregnancy is confirmed
  • 50% increase if no thyroid tissue (congenital hypothyroidism, post total thyroidectomy, post radioactive iodine ablation)

• Thyroid function monitored q four to six weeks until the TSH level is stable, then q 8 weeks with a final check at about 28 to 32 weeks’ gestation

• Postpartum
  • Levothyroxine dose returned to the prepregnancy dose
  • Thyroid function should be checked two to three months' postpartum

Hypothyroidism
Effects on Fetus and Infant

• No evidence of thyroid dysfunction

• Mass screening to minimize sequelae of congenital hypothyroidism (1/4,000 infants) and prompt aggressive T4 replacement
  • Sequelae can be prevented with treatment in the first few weeks of life
Nodular Thyroid Disease

- Evaluate by ultrasound and fine-needle aspiration or tissue biopsy
- Avoid radioiodine scanning
- (+) thyroid cancer
  - Differentiated (papillary or follicular) – surgery can be delayed until postpartum period as such a delay is unlikely to affect long-term prognosis
  - Advanced differentiated, medullary, or poorly differentiated – surgery in the second trimester may be considered

Postpartum Thyroid Dysfunction

*Postpartum Thyroiditis*

- Autoimmune inflammation
- Affects 5-10% of women in postpartum period
- Presents as new-onset:
  - Painless hypothyroidism (25%) or
  - Transient thyrotoxicosis (50%) or
  - Thyrotoxicosis followed by hypothyroidism within one year postpartum
  - Eventual return to euthyroidism
- Transient and recurrent in subsequent pregnancies
  - 70% risk of recurrence
- May occur after pregnancy loss
Postpartum Thyroid Dysfunction

Postpartum Thyroiditis

**Risk**
- (+) TPOAb – 50% risk of developing
- Past history of PP Thyroiditis – 70% risk of developing

**Treatment unclear**
- Permanent hypothyroidism is uncommon
- Thyrotoxicosis and hypothyroidism are mild
- Toxic phase – no antithyroid medications
- Check TSH q 2 months AFTER toxic phase
- May try to wean from replacement at 6-12 months after initiating treatment

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Postpartum Thyroiditis

*Diagnosis/Screening*

**Document new-onset abnormal levels of TSH or FT₄ or both**

**Screening with TFTs and antimicrosomal antibodies in asx women NOT warranted**
Could she have Graves’ Disease?

• This is the **main** differential diagnosis
  • (+) TRAb
  • Signs – Goiter with a bruit or ophthalmopathy
  • Uncertainty about diagnosis – technetium uptake scan
    • Breastfeeding – breastmilk expressed and discarded during scan + 48 hours afterwards
• (+) thyrotoxicosis > 6months postpartum – Graves’ is most likely diagnosis

Antithyroid medications are needed?

• Graves’ disease in Breastfeeding mothers
  • Lowest effective dose
  • Ingest FOLLOWING a breastfeed
• Doses – safe in breastfeeding; less than 1% of parent drug transferred to breastmilk
  • PTU 300 mg
  • Methimazole 20 mg
What can we say -

- TSH goal in pregnancy < 3.0
- Levothyroxine is indicated for subclinical hypothyroid with (+) thyroid peroxidase antibodies
- Gravid women with subclinical hypothyroidism not treated
  - Check TSH and T4 q 4 weeks until 16-20 weeks and then AT LEAST once between 26 and 32 weeks
- No radioactive iodine scanning or ablation

Best Practice Recommendations

- Women at high risk of thyroid dysfunction should undergo screening with measurement of thyroid stimulating hormone (TSH) levels in early pregnancy.
- If the TSH level is 2.5mIU/L or more on early pregnancy screening, levels of thyroid peroxidase antibodies should be measured to identify women who may benefit from treatment for subclinical hypothyroidism.
- Transient gestational hyperthyroidism is a common cause of mild hyperthyroidism in early pregnancy. Referral of the patient to an endocrinologist is recommended if TSH levels remain persistently undetectable and/or T3 or T4 levels are elevated and/or TSH receptor antibodies (TRAb) are positive.
- Women with active Graves’ disease or a history of Graves’ disease treated with surgery or radioactive iodine may be at risk of fetal hyperthyroidism. If TRAb level is elevated at 18 to 22 weeks’ gestation, endocrinology and maternal-fetal medicine input are required.
Speaker Contact Information

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References

Thank you
Questions
Hyperthyroidism and Hypothyroidism: The Ups and Downs

Edward Mayeaux, MD, FAAFP, DABFM, DABPM

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The content of my material/presentation in this CME activity will include discussion of unapproved or investigational uses of products or devices as indicated: Organic iodide radiographic contrast agents used block peripheral conversion of T4 to T3 and inhibit release.

Edward Mayeaux, MD, FAAFP, DABFM, DABPM

Professor and Chair, Department of Family and Preventive Medicine/Professor of Obstetrics and Gynecology, University of South Carolina School of Medicine, Columbia

Dr. Mayeaux lives and practices in Columbia, South Carolina. He has received the American Society for Colposcopy and Cervical Pathology (ASCCP) Award of Merit four times and has also received numerous faculty teaching awards. He focuses on women's health and skin diseases, noting that the most important trends in the field are the rise and fall of methicillin resistant Staphylococcus aureus (MRSA); changes in Pap test recommendations and follow up; and changes in human papillomavirus (HPV) testing recommendations. Dr. Mayeaux considers keeping up with the rapidly changing knowledge base in medicine and physician burnout to be family medicine's most critical challenges. Other professional interests include health care quality, preventive medicine, and returning joy to medical practice.
Learning Objectives

1. Develop a screening protocol to identify patients with risk factors for developing hypo/hyper-thyroidism, particularly pregnant patients or those planning to become pregnant.

2. Order appropriate laboratory and radiologic tests to diagnose hypo/hyper-thyroidism based on symptomatology.

3. Prescribe appropriate therapy for patients with hypo/hyper-thyroidism symptomatology and monitor patients accordingly.

4. Identify the clinical signs, symptoms and required laboratory tests for diagnosing acute viral thyroiditis.

5. Recognize indications for referral and possible admission and coordinate care and follow-up as necessary.

AES Question
Poll Question 1

Which of the following is NOT a common symptom of hyperthyroidism?

A. Emotional lability
B. Weakness
C. Palpitations
D. Diarrhea

Hyperthyroidism Symptoms

- Anxiety, emotional lability
- Weakness, tremor, "apathetic thyrotoxicosis"
- Palpitations
- Heat intolerance, increased perspiration
- Weight loss despite normal or ↑ appetite
  - Hyperdefecation (not diarrhea), urinary frequency, oligomenorrhea or amenorrhea, gynecomastia and erectile dysfunction

Hyperthyroidism Signs

- **Hyperactivity** and rapid speech
- Sympathetic hyperactivity
- **Warm, moist skin** and/or thin fine hair
- **Tachycardia** and/or systolic hypertension
- Tremor
- Proximal muscle weakness
- **Hyperreflexia**


Thyroid Regulation

T3 receptors in
- Skeletal muscle
- Cardiac muscle
- Bone
- Liver

Image courtesy of E.J. Mayeaux, Jr., MD
Serum T4 and T3

- Both are highly bound to proteins
- **Total** measures free + bound
  - Normal range is variable between labs
- Serum free T4 and free T3
  - **Free hormone** is available for **uptake into cells** and interaction with nuclear receptors
  - Bound hormone is **storage pool**
  - T4 10x more bound


Subclinical Hyperthyroidism

- Normal serum free T4 & T3 with a **suppressed TSH level**
- **Symptoms** mild and nonspecific
- Often toxic nodular goiter or mild Graves ds
- Associated with a **2-fold increase** in the risk of **atrial fibrillation** in older persons and **decreased bone mineral density** in postmenopausal women

Drugs Causing Hyperthyroidism

• Stimulation of thyroid hormone - iodine, amiodarone
• Immune dysregulation - interferon-alfa, interleukin-2, denileukin diftitox, ipilimumab, alemtuzumab
• ↓ TBG - androgens, danazol, glucocorticoids, slow-release niacin (nicotinic acid), l-asparaginase
• ↑ TBG - estrogens, tamoxifen, raloxifene, methadone, 5-fluouracil, clofibrate, heroin, mitotane
• ↓ T4 binding to TBG - salicylates, salsalate, furosemide, heparin (via free fatty acids), certain NSAIDs
• Increased T4 clearance - phenytoin, carbamazepine, rifampin, phenobarbital
• ↓ TSH secretion - dobutamine, glucocorticoids, octreotide
• Impaired conversion of T4 to T3 - amiodarone, glucocorticoids, contrast agents for oral cholecystography, PTU, propranolol, nadolol

Hyperthyroidism Diagnosis

• T3-toxicosis - Graves' ds or nodular goiter
  • ↓ TSH, ↑ serum T3 > ↑ serum T4
    • ↑ thyroidal T3 secretion and ↑ extrathyroidal conversion T4
  • In early disease, patient may have normal serum T3 and free T4 levels
Graves’ Disease Signs

• Exophthalmos
• Periorbital & conjunctival edema
• Limitation of eye movements
• Infiltrative dermopathy (pretibial myxedema)


Graves’ Disease Dx

• Clinical signs
• Measurement of thyrotropin receptor antibodies
  • Sensitivity/specificity = 97/99% for Graves
• Radioactive iodine uptake
• Quantitative thyroid blood flow by ultrasonography (skill dependent)

Thyroid Scan

• Graves’ disease produces a more uniform increased uptake

Hyperthyroidism Diagnosis

• T4-toxicosis - ↓ TSH,
  ↑ free T4, & normal T3
  • Hyperthyroidism in pts with concurrent nonthyroidal illness that ↓ extrathyroidal conversion of T4 to T3
  • Despite the nonthyroidal illness, patients remain hyperthyroid and with ↓ serum TSH
Hyperthyroidism Diagnosis

**Signs or symptoms**

<table>
<thead>
<tr>
<th>Serum TSH &amp; fT4</th>
<th>Primary hyperthyroidism</th>
<th>Secondary hyperthyroidism</th>
<th>Image pituitary gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ TSH ↑ fT4</td>
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<td></td>
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<tr>
<td>↓ TSH Ni fT4</td>
<td></td>
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</table>

**Thyroid uptake**

- Low
  - Exogenous hormone
  - Thyroiditis, iodine exposure, extraglandular production
- High
  - Thyroglobulin

**Serum fT3**

- High T3
  - T3 toxicosis
  - Graves or nodular goiter
- Ni T3
  - Subclinical hyperthyroid
  - Resolving hyperthyroid
  - Medication
  - Pregnancy
  - Nonthyroid illness

AES Question
Poll Question 2

True statements about the treatment of hyperthyroidism include which of the following?

A. Beta blockers treat palpitations and tachycardia but not other symptoms
B. Iodides are contraindicated because of increased hormone synthesis
C. Methimazole is preferred in all non-allergic patients due to lower cost, longer half-life, and lower incidence of hematologic side effects
D. PTU is preferred in pregnancy

Hyperthyroidism Treatment

• **Beta blockers** *(propranolol)* 10 - 20 mg Q 6 hours
  • Prompt relief of adrenergic S/S (tremor, palpitations, and nervousness)
• **CCBs** *(diltiazem)* used to reduce heart rate
• **Iodides** block peripheral conversion of T4 to T3 and inhibit release
  • Adjunctive therapy before emergency nonthyroid surgery if beta blockers are ineffective and to reduce gland vascularity before Graves’ surgery
  • Iodides are not used routinely because of paradoxical increases in hormone release with prolonged use
  • Organic iodide **radiographic contrast** agents (1 g per day for up to 12 weeks) used more commonly

Antithyroid Drugs

- Interfere with iodine organification
  - **Methimazole** (15-30 mg/day) drug of choice in nonpregnant patients - lower cost, longer half-life, and lower incidence of hematologic side effects but associated with rare congenital abnormalities
  - **PTU** (100 mg TiD maintenance of 100-200 mg daily) is preferred during the first trimester of pregnancy
- Remission rates of up to 60% when therapy continued for 2 years
- Relapse can occur in up to 50% of patients
  - Relapse more likely in patients who smoke, have large goiters, or had elevated thyroid-stimulating antibody levels at end of therapy


Radioactive Iodine

- **US tx of choice** for Graves’ disease and toxic nodular goiter
- Contraindicated in pregnant patients!!
- It is inexpensive, highly effective, easy to administer, and safe
- Theoretical risk of cancer of the thyroid, leukemia, or genetic damage in future offspring of pregnant women but long-term follow-up of patients has not validated these concerns
- Higher-dose ablative therapy increases the chance of successful treatment
  - Allows resulting early hypothyroidism to be diagnosed and treated while the patient is undergoing close monitoring
Hyperthyroidism in Pregnancy

• Overt hyperthyroidism relatively uncommon during pregnancy
  • Occurs in 0.1 to 0.4 percent of all pregnancies [1,2]

• During pregnancy: ↑TBG, ↑ total T4 / T3 but normal free T4 / T3

• Clinical manifestations - same
  • Many are same as nonspecific symptoms associated with pregnancy

Hyperthyroidism in Pregnancy

Overt hyperthyroidism associated with:¹
• Spontaneous abortion
• Premature labor
• Low birth weight
• Stillbirth
• Preeclampsia
• Heart failure

Subclinical hyperthyroidism – no adverse pregnancy outcomes²

Common Causes, Diagnosis, and Initial Management of Hypothyroidism

AES Question
Poll Question 3

What is the most common cause of hypothyroidism in the US?

A. Congenital abnormalities
B. Autoimmune disease
C. Iodine deficiency
D. Infiltrative diseases
E. Neck irradiation

Hypothyroidism

• Failure of gland to produce sufficient hormone to meet body metabolic demands

• ~1/300 persons in U.S.¹
  • Prevalence increases with age
  • Higher in females than in males²
  • ~13 million Americans have undiagnosed disease³

Untreated Hypothyroidism

• Can contribute to
  • Hypertension
  • Dyslipidemia
  • Infertility
  • Cognitive impairment
  • Neuromuscular dysfunction


Drugs Causing Hypothyroidism

• ↓ thyroid hormone synthesis and/or release - thionamides, lithium, perchlorate, aminogluthethimide, thalidomide, and iodine and iodine-containing drugs including amiodarone, radiographic agents, expectorants, kelp tablets, potassium iodine solutions (SSKI), povidone-iodine (Betadine) douches, topical antiseptics
• ↓ absorption of T4 - cholestyramine, colestipol, colesevelam, aluminum hydroxide, calcium carbonate, sucralfate, iron sulfate, raloxifene, omeprazole, lansoprazole, and possibly other medications that impair acid secretion, sevelamer, lanthanum carbonate, and chromium; malabsorption syndromes
• Immune dysregulation - interferon-alfa, interleukin-2
• Suppression of TSH - dopamine
• ↑ type 3 deiodination - sorafenib
• ↑ T4 clearance and suppression of TSH - bexarotene
Hypothyroidism

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tr>
<td>Fatigue</td>
<td>Bradycardia</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>Cognitive impairment</td>
<td>Increased CRP, CK</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>Coarse facies</td>
<td>Hyperprolactinemia</td>
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<td>Constipation</td>
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<td>Effusions</td>
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</tbody>
</table>

Subclinical Hypothyroidism

- Biochemical diagnosis
- Normal-range free T4 and elevated TSH
  - May or may not have symptoms
  - On repeat testing, TSH may spontaneously normalize
- Incidence ranges from 3 to 15%
  - Increasing with age, female sex, and low iodine status
- Associated with progression to overt hypothyroidism
  - Especially with ↑ thyroid peroxidase abs

Hypothyroidism – Screening

• AAFP supports USPSTF - insufficient evidence \(^1\)
  • No asymptomatic adult screening
  • All newborns screened
• Consider screening with risk factors
  • Hx of autoimmune disease
  • Hx head/neck irradiation, radioactive iodine
  • Goiter
  • Family hx thyroid disease
  • Drugs known to influence thyroid function

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Hypothyroidism Diagnosis

![Flowchart of hypothyroidism diagnosis](chart.png)

- **Serum TSH**
  - TSH > 5.5 mIU/L
    - Serum free T4
      - Low Free T4
        - Primary hypothyroidism
  - TSH in normal range
    - NI Free T4
      - Subclinical hypothyroidism
      - Confirm TSH/T4 in 2-3 months
  - TSH < 0.35 mIU/L
    - High Free T4
      - Central hyperthyroidism
    - Consider hyperthyroid state

Hypothyroidism Treatment

• Most patients require **lifelong therapy**
• Once-daily synthetic thyroxine T4
• Normal thyroid makes T4 and T3
  • T4 produced in greater amounts
  • T3 biologically active
    • ~80% T3 derived from peripheral T4 conversion
  • T3 preps have **short half-life**
• Do not switch generics or switch to/from Brand


---

Hypothyroidism Treatment

• Start **levothyroxine**
  • Healthy adults is **1.6 mcg/kg/day**
    • Morning or evening 30 minutes before eating
    • No calcium or iron supplements within 4 hours
    • **Poor adherence** most common cause of ↑ TSH
  • Older or cardiac disease – 25-50 mcg/day then ↑ 25 mcg Q3-4 wks
• **Subclinical hypothyroidism**
  • TSH < 10 mIU/L or Age > 70 years: based on patient
    • 50 mcg/day, ↑ by 25 mcg Q6 wks
    • TSH ≥ 10 mIU/L: adult dosage

Reverse T3?

• rT3 is the stereoisomer T3
• Most rT3 is formed by peripheral deiodination of T4 (thyroxine)
• In hospitalized or sick patients with low T3, elevated rT3 is consistent with "sick euthyroid" syndrome
  • Finding an elevated rT3 level in a critically ill patient helps exclude a diagnosis of hypothyroidism
• The rT3 is high with propylthiouracil, ipodate, propranolol, amiodarone, dexamethasone, and halothane
• Some theorize rT3 competes with T3 binding – minimal evidence

Hypothyroidism in Pregnancy

• Women need more thyroid hormone in pregnancy
  • ~75 – 85% of women with preexisting hypothyroidism need a higher dose of T4
  • Increase ~5th week of gestation
• All newborns should be screened
• Consider referrals if positive

Thyroiditis

Hashimoto Thyroiditis

- Nontender goiter, hypothyroidism, and an elevated thyroid peroxidase antibody level
- Rarely thyrotoxicosis secondary to alternating stimulating & inhibiting thyroid autoantibodies
- Measure serum TSH and TPO antibody levels
- Elevated TSH and low free T4 levels
  - Levothyroxine starting with 1.6 mcg/kg/day
  - Incremental changes made every 10 to 12 weeks

Suppurative Thyroiditis

- Thyroid pain, high fever, leukocytosis, and cervical lymphadenopathy; focal inflammation
- Compressive symptoms such as dysphonia or dysphagia; patients may assume a posture to limit neck extension
- Palpation may reveal focal or diffuse swelling of the thyroid
- Overlying skin warm and erythematous
- Multiple infectious organisms, most commonly bacterial. Streptococcus pyogenes; Staphylococcus aureus and Pneumococcus are among the most common isolates

Subacute Thyroiditis

- Thyroid pain, hyperthyroidism or hypothyroidism
- Postviral
- Thyroid function tests; elevated TPO antibody levels; low radioactive iodine uptake in the hyperthyroid phase
- Euthyroidism generally by 18 months - rarely recurs
  - Up to 15% of patients become permanently hypothyroid
- Beta blockers for significant hyperthyroid symptoms
- Levothyroxine for symptomatic hypothyroidism
- NSAIDS for pain

Riedel (Fibrous) Thyroiditis

- Very firm goiter
- Compressive symptoms (dyspnea, stridor, dysphagia), which appear disproportionate to the size of the thyroid
- Hypocalcemia may occur - fibrosis of the parathyroid glands
- Viral +/- Autoimmunity


Thyroiditis Treatment

- Initial hyperthyroid phase - Beta blockers for symptoms
- Subsequent hypothyroid phase, levothyroxine should be considered in women with a serum thyroid-stimulating hormone level greater than 10 mIU per L, or in women with a thyroid-stimulating hormone level of 4 to 10 mIU per L who are symptomatic or desire fertility.
- Treatment with high-dose NSAIDs is directed toward relief of thyroid pain

Thyroid Nodules

AES Question
Poll Question 4

True statements about thyroid nodules include which of the following?

A. About ½ are malignant  
B. FNA gives best nonsurgical diagnosis  
C. They are rarely associated with multinodular goiter  
D. Cancers are more common in the 40- to 50-year-old group

Thyroid Nodules

• 4-7% population  
• Most are benign  
  • 1.5-17% malignant  
• ~23% are actually dominant nodules in a multinodular goiter  
• ~1,300 US deaths

Types of Thyroid Nodules

- Adenoma
- Macrofollicular adenoma (simple colloid)
- Microfollicular adenoma (fetal)
- Embryonal adenoma (trabecular)
- Hürthle cell adenoma
- Atypical adenoma
- Adenoma with papillae
- Signet-ring adenoma

- Carcinoma
- Cyst
- Colloid nodule
- Inflammatory thyroid disorders
  - Subacute thyroiditis
  - Chronic lymphocytic thyroiditis
  - Granulomatous disease
- Developmental abnormalities
  - Dermoid
  - Rare unilateral lobe agenesis

Higher Prevalence of Cancer

- Children
- Adults < 30 years or > 60 years old
- Patients with a history of head and neck irradiation
- Patients with a family history of thyroid cancer
Thyroid Nodule Diagnosis

- **Solitary thyroid nodule**
  - **Serum TSH**
  - **Euthyroid**
  - **Hot nodule - Tx**
  - **Cold nodule**
  - **Hyperthyroid**

  - **FNA**
  - **Insufficient**
    - **Solid**
    - **Cystic**
      - **Recur/Persist**
      - **Observe**
  - **Benign**
    - **Repeat in six months**
  - **Suspicious**
    - **Total or partial thyroidectomy**

Diagnostic Thyroid/Neck US

- Thyroid sonography with survey of cervical lymph nodes should be performed in all patients with known or suspected nodules (Strong recommendation, High-quality evidence)

- Report should convey
  - Nodule size (in 3 dimensions) & location (e.g., right upper lobe)
  - Description of features (solid, cystic proportion, or spongiform)
  - Echogenicity, margins, presence and type of calcifications, vascularity
  - Sonographic pattern defines malignancy risk and with nodule size, guides FNA decision-making

Haugen BR, et al. Thyroid 2016 26: 1-133
Best Practice Recommendations

• Methimazole is the drug of choice in nonpregnant patients
• PTU is preferred during the first trimester of pregnancy
• Most hypothyroidism treated with once-daily synthetic thyroxine
• Most thyroid nodules are benign and FNA is often best way to make diagnosis
Answers

1. D
2. D
3. B
4. B

Questions
Prediabetes Screening and Management: A Spoonful of Prevention!
Get Ahead of Diabetes

Kate Kirley, MD, MS
Neha Sachdev, MD

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The content of my material/presentation in this CME activity will include discussion of unapproved or investigational uses of products or devices as indicated:

• Will include discussion of Metformin for the indication of prediabetes treatment. This is a non-FDA approved (off-label) use of Metformin despite high quality evidence of efficacy and safety.

Kate Kirley, MD, MS

Director of Chronic Disease Prevention, Improving Health Outcomes group, American Medical Association (AMA), Chicago, Illinois

After graduating from the University of Michigan Medical School, Ann Arbor, Dr. Kirley completed her family medicine residency at the University of Illinois at Chicago (UIC)/Illinois Masonic Medical Center. She subsequently completed a research fellowship at the University of Chicago. Currently, she serves as the lead clinician for the AMA’s diabetes prevention initiatives. Prior to joining the AMA, Dr. Kirley was a practicing family physician and health services researcher at NorthShore University HealthSystem, and a clinical assistant professor in the University of Chicago’s Department of Family Medicine. She also served as assistant director of NorthShore’s Quality and Patient Safety Fellowship and as assistant director of the Ambulatory Primary Care Innovations Group, a practice-based research network.
Neha Sachdev, MD

Director of Health Systems Relationships in Improving Health Outcomes, American Medical Association, Chicago, Illinois

In her role, Dr. Sachdev works with physicians, care teams, and health care organizations to implement evidence-based strategies for the prevention of cardiovascular disease. Prior to joining the American Medical Association (AMA), she was a core faculty attending physician at the Virtua Health family medicine residency program. After earning her medical degree from Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania, Dr. Sachdev completed her family medicine residency training at McGaw Medical Center of Northwestern University and Erie Family Health Center in Chicago, Illinois, as part of the Teaching Health Center Graduate Medical Education (THCGME) program. She holds a Bachelor of Arts degree in Hispanic Studies and Health and Societies from the University of Pennsylvania.

Learning Objectives

1. Recognize the pathogenesis, progression risks, and management strategies for patients with pre-diabetes.

2. Establish evidence-based systematic protocols for screening patients for diabetes mellitus.

3. Use evidence-based recommendations and guidelines to order appropriate diagnostic tests to diagnose and confirm the etiology of diabetes.

4. Counsel patients on lifestyle modifications they can make to reduce their risk for developing diabetes and comorbidities, including diet, exercise, smoking cessation and alcohol consumption.
Associated Sessions

• (PBL) Prediabetes Screening and Management: A Spoonful of Prevention! Get Ahead of Diabetes

Audience Engagement System
Epidemiology and Pathogenesis
Diagnosed Diabetes, Age-Adjusted Percentage, Adults with Diabetes - U.S. States

Disclaimer: This is a user-generated report. The findings and conclusions are those of the user and do not necessarily represent the views of the CDC.

Source: www.cdc.gov/diabetes/data

Prediabetes in the US

~1 out of 3 adults affected

9 out of 10 are unaware

Poll Question #1

Which of the following is not a risk factor for abnormal glucose metabolism?

A. African American race
B. Obesity
C. Hypertension
D. Smoking
E. Alcohol use

Pathogenesis

Complex, incompletely understood

Excess adipose tissue → Decreased insulin sensitivity → Progressive loss of beta cell insulin secretion

Genes → Environment → Lifestyle → Social Determinants → Microbiome → ???
Risk Factors for Type 2 Diabetes

- Adiposity
  - BMI, waist circumference
- Lifestyle factors
  - Physical activity level, sedentary time, smoking status
- Medical history
  - Gestational diabetes, metabolic syndrome
- Dietary factors
  - Dietary pattern, sugar sweetened beverage intake
- Other factors
  - Psychosocial factors, biomarkers

+ family history and racial/ethnic background


Social Determinants and Risk

- Low early life socioeconomic conditions
  - 1.54 OR for prediabetes
  - 1.46 OR for type 2 diabetes

- Low adulthood socioeconomic conditions
  - 1.67 OR for prediabetes
  - 3.43 OR for type 2 diabetes

Poll Question #2

A 55 yo woman comes to see you for an annual wellness visit. She last had a fasting glucose test checked 4 years ago that was normal. What is the most appropriate way to screen her for abnormal glucose?

A. Fasting plasma glucose
B. Hemoglobin A1c
C. 2-hour glucose tolerance test
D. No screening – she is up to date

Identification and Screening
Guidelines/Recommendations/Clinical Resources Related to Diabetes Prevention

<table>
<thead>
<tr>
<th>Organization</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Preventive Services Task Force</td>
<td>Abnormal Glucose Screening Recommendation (2015)*</td>
</tr>
<tr>
<td>American Diabetes Association</td>
<td>Standards of Medical Care in Diabetes (2019)</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists/American College of Endocrinology</td>
<td>Clinical Practice Guideline for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)</td>
</tr>
<tr>
<td></td>
<td>Comprehensive Type 2 Diabetes Management Algorithm (2019)</td>
</tr>
<tr>
<td>Community Preventive Services Task Force</td>
<td>Diabetes Prevention and Control: Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among People at Increased Risk (2015)</td>
</tr>
<tr>
<td>National Diabetes Education Program</td>
<td>Guiding Principles for the Care of People With or At Risk for Diabetes (2018)</td>
</tr>
</tbody>
</table>

*in process of being updated

United States Preventive Services Task Force (USPSTF) Abnormal Glucose Screening Recommendation

Grade B recommendation

- Screen all adults ages 40-70 AND who have a BMI ≥ 25
- Screen with a fasting glucose, hemoglobin A1C or oral glucose tolerance test

USPSTF standards suggest testing patients every 3 years

United States Preventive Services Task Force (USPSTF)

Abnormal Glucose Screening Recommendation

Consider testing adults of a lower age or BMI if risk factors present.

**Family history**
- Family history of type 2 diabetes includes first-degree relatives (a person's parent, sibling or child)

**Medical history**
- Gestational diabetes
- Polycystic ovary syndrome

**Racial & ethnic minorities**
- African Americans
- American Indians
- Alaskan Natives
- Asian Americans
- Hispanics or Latinos
- Native Hawaiians or Pacific Islanders


ADA Standards of Medical Care in Diabetes

- Informal risk assessment or validated risk assessment tool should be considered in asymptomatic adults to guide on need for diagnostic testing

- Consider testing adults at any age with BMI ≥25 (≥23 for Asian Americans) and one or more risk factors
  - First degree relative with DM
  - High-risk race/ethnicity
  - History of CVD
  - HTN
  - HDL <35 mg/dL and/or Triglycerides >250mg/dL
  - Women with PCOS
  - Physical inactivity
  - Conditions associated with insulin resistance

ADA Standards of Medical Care in Diabetes

• Begin testing all adults at age 45
• Equally appropriate to use A1C, fasting plasma glucose or 2 hour oral glucose tolerance for testing
• If initial results are normal, repeat testing at a minimum of 3 year intervals
• Women with a history of gestational diabetes should have lifelong testing at least every 3 years


AACE/ACE Clinical Practice Guidelines

Risk factors for prediabetes/type 2 diabetes: Criteria for testing in asymptomatic adults

<table>
<thead>
<tr>
<th>Age ≥45 years without other risk factors</th>
<th>CVD or family history of type 2 DM</th>
<th>BMI that is overweight or obese*</th>
<th>Sedentary lifestyle</th>
<th>Member of at-risk racial or ethnic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL &lt; 35 and/or Triglycerides &gt;250</td>
<td>IGT, IFT or metabolic syndrome</td>
<td>PCOS, Acanthosis Nigricans, NAFLD</td>
<td>Hypertension (BP &gt;140/90 or on therapy)</td>
<td>History of gestational diabetes or delivery of baby &gt; 4kg</td>
</tr>
<tr>
<td>Antipsychotic therapy for schizophrenia/bipolar disease</td>
<td>Chronic glucocorticoid exposure</td>
<td>Sleep disorders in presence of glucose intolerance including OSA, chronic sleep deprivation and night shift occupation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*At-risk BMI may be lower in some ethnic groups; consider using waist circumference or other factors

BMI = body mass index; BP = blood pressure; CVD=cardiovascular disease; HDL-C = high density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NAFLD = nonalcoholic fatty liver disease; PCOS = polycystic ovary syndrome

AACE/ACE Clinical Practice Guidelines

- Testing should be considered in all adults who are obese and all adults who are overweight with additional risk factors
- Individuals with 2 or more risk factors - consider annual screening
- Individuals at risk with glucose values in the normal range - screen every 3 years
- Metabolic syndrome (based on NCEP criteria) should be considered a prediabetes equivalent
- A1C should be used only for screening - diagnosis of prediabetes should be confirmed with glucose testing

Acceptable Laboratory Tests

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Advantages/Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>Convenient&lt;br&gt;Accuracy of test is monitored&lt;br&gt;Representative of glucose over months&lt;br&gt;Cost (not covered by Medicare)&lt;br&gt;Relationship with glycemia can be altered by certain conditions</td>
</tr>
<tr>
<td>FPG</td>
<td>Widely available&lt;br&gt;Biological variability - can be affected by recent activities of patient&lt;br&gt;Often hard to assess if previous lab results were fasting&lt;br&gt;Variability amongst lab measurement and with blood source</td>
</tr>
<tr>
<td>OGTT</td>
<td>Assesses response to glucose challenge - sensitive indicator&lt;br&gt;Requires time and extensive patient preparation&lt;br&gt;Expensive</td>
</tr>
</tbody>
</table>

Management of Abnormal Glucose

Prediabetes Identification

*ICD10 code: R73.03*
Poll Question #3

Your 55 year-old patient has a lab result consistent with prediabetes. What do you do next?

A. Counsel her to lose weight
B. Document the diagnosis and educate the patient about her diagnosis
C. Refer her to an intensive weight loss or lifestyle change program
D. Prescribe Metformin
E. None of the above

Diabetes Prevention Program RCT

• NIH-funded 3-arm RCT (N=3234) comparing placebo vs metformin vs intensive lifestyle counseling
  – Low calorie, low fat diet plus moderate physical activity
  – Program goal: ≥7% weight loss

• The lifestyle intervention reduced the incidence by 58% compared to placebo
  – Metformin reduced the incidence by 31% compared to placebo

United States Preventive Services Task Force (USPSTF)
Abnormal Glucose Screening Recommendation

Offer or refer patients with abnormal glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity

National Diabetes Prevention Program
lifestyle change program

- Designed to slow and prevent the development of type 2 diabetes
- Comprehensive program focused on weight loss through increased physical activity and diet and behavior modification
- Can be delivered in-person, online or via distance learning
- Can be delivered in community or clinical settings

Emphasis is on prevention and empowerment through a personal action plan
Trained lifestyle coaches teach group classes; coaches can be health professionals but do not have to be
National Diabetes Prevention Program lifestyle change program

• Quality assurance through the Centers for Disease Control and Prevention
• CDC is mandated by Congress to oversee the program
• Program providers apply for recognition to the CDC

Eligibility for a DPP lifestyle change program

✓ BMI ≥25 (≥23 if Asian American)

AND

✓ One of the following
  □ Prediabetes diagnosis
  OR
  □ History of GDM
  OR
  □ Elevated risk score (ADA or doihaveprediabetes.org screener)

*do not need a laboratory test; participants can self-refer
Coverage for DPP lifestyle change programs

- Medicare coverage began April 2018
- Medicaid coverage in 6 states, with ongoing pilots in 4 states
- State employee coverage in 20 states with 4 pilots
- Growing private insurers offering coverage (Anthem, Cigna)

The Role of Physicians and Care Teams in Diabetes Prevention

- Identify patients at risk for type 2 diabetes
- Engage in shared decision-making with patients and manage with evidence-based treatment option
- Support individuals in their treatment plan

Everyone with prediabetes should be aware of the condition and receive treatment.
Tools for Diabetes Prevention

- Patient risk assessment
- Patient education handouts
- Clinical protocols
- Relevant ICD10 and CPT codes
- Evidence summary

........and more to come!

www.amapreventdiabetes.org

Information about DPP lifestyle change programs

CDC’s National Diabetes Prevention Program

To locate a program
https://nccd.cdc.gov/DDT_DPRP/Programs.aspx
Access Challenges

No DPP lifestyle change program near you?  
*Explore the possibility of starting a program within your organization*

Patients with transportation or time limitations?  
*Refer patients to CDC-recognized digital programs*

Digital DPP lifestyle change programs

- **Participant experience**
  - Complete curricula on their own time (asynchronously)
  - Can use smart scales to monitor weight or wearables to track activity
  - Personalized health coaching via messaging
  - Group support on online platform
- **Effective for achieving clinically meaningful weight loss (5% of body weight)**
- **Recognized by CDC; currently over 25 providers**
  - Examples: Noom, Omada, Livongo

Metformin

- Not FDA-approved for diabetes prevention
- High-quality evidence demonstrates effectiveness
- Consider in those with
  - BMI $\geq 35$ kg/m$^2$
  - Age $<60$
  - Women with h/o GDM
  - Worsening glucose despite lifestyle intervention


Poll Question #4

Your patient is overwhelmed by her diagnosis of prediabetes. She is hearing that she has to lose weight and make changes but she's tried before with no success. What can you tell her?

A. You can reduce your risk by losing only 5% of your body weight
B. Your risk of diabetes is high if you don't change
C. You can take a pill
D. We can keep monitoring you to see if it gets worse
Common Physician Concerns

- I’m not really sure what to tell my patients
- Even if I counsel them, my patients still fail to change
- I don’t have enough time

Structured Counseling Strategies

<table>
<thead>
<tr>
<th>Transtheoretical (Stages of Change)</th>
<th>Assesses patients’ motivation for change; focused on specific health behavior and adherence; can guide choice of subsequent counseling model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Five A’s (Ask, Advise, Assess, Assist, Arrange)</td>
<td>Stepwise approach, assumes patients lack complete knowledge and will respond to direct advice; impact of each A varies</td>
</tr>
<tr>
<td>FRAMES (Feedback, Responsibility of Patient, Advice to Change, Menu of Options, Empathy, Self-efficacy Enhancement)</td>
<td>Precursor to MI, provides new information; encourages personalized selection to treatment, shared decision-making</td>
</tr>
<tr>
<td>Motivational Interviewing</td>
<td>Recognizes and acknowledges ambivalence to change, provides systematic approach to increase motivation; relates health behavior to patient values</td>
</tr>
</tbody>
</table>
Ask/Assess -> Assist/Refer

Assess

Ask

Advis

Assist

Arrange

Risk Assessment and/or Lab Testing

Shared Decision-Making and Referrals

Counseling Patients- Key Messages

• Your blood glucose is higher than normal but not at the level of diabetes. This condition is called prediabetes.

• Prediabetes is a serious condition: It poses a high risk of eventually progressing to diabetes and raises your risk of other medical conditions.

• Prediabetes is treatable and can be reversible
  • The goal is to lose a modest amount of weight (5-7% of body weight) and lead a healthier lifestyle
  • A lifestyle change program can support you to do this and help you make lasting healthy behavior changes

Practice Recommendations for Physicians & Care Teams

• Involve the entire care team in identifying patients at risk for abnormal glucose and those with prediabetes
  – Diagnose those who have the condition and document the diagnosis

• Utilize the electronic health record
  – Establish a prediabetes registry
  – Incorporate clinical decision support
  – Provide regular reports to care teams

• Implement structured counseling strategies and shared decision-making

• Monitor patients
  – Schedule follow-up to support patient engagement in lifestyle change
  – Repeat labs/order additional tests as needed

Contact Information

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• Neha Sachdev
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Questions
Vitamin Deficiencies: Common Nutrient Deficiencies in Practice

George Edward Guthrie, MD, MPH, CDE, FAAFP, FACLM

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George Edward Guthrie, MD, MPH, CDE, FAAFP, FACLM

Assistant Director, Florida Hospital Family Practice Residency, Winter Park

Dr. Guthrie graduated from medical school at Loma Linda University, California, in 1981. He completed his family medicine residency at Hinsdale Hospital, Illinois. Following residency, he practiced in Guam for seven years, where he was chiefly responsible for starting a new AAFP chapter. Due to his interest in the lifestyle treatment of chronic disease, particularly diabetes, he returned to Loma Linda University to earn his Master of Public Health (MPH) degree, with an emphasis on nutrition. He proceeded to teach at Loma Linda University School of Medicine and in the nutrition department of the Loma Linda University School of Public Health. Later, he provided outpatient services in a rural clinic in northern California for seven years and then spent nearly five years as the medical and program director of the Lifestyle Center of America near Ardmore, Oklahoma.

For the past 12-plus years, Dr. Guthrie has taught in the family medicine residency program at Florida Hospital, Winter Park. He has helped pilot and/or develop several patient-focused lifestyle change programs, including the Complete Health Improvement Project, CREATION Health, and the Wellspring Diabetes Program. Most recently, he completed a term as president of the American College of Lifestyle Medicine (ACLM), a rapidly growing professional organization for caregivers focused on non-drug therapy for chronic lifestyle-related disease.
Learning Objectives

1. Identify patients at risk of vitamin deficiency (e.g., D, B12), or at risk for potential vitamin-drug interactions.

2. Counsel patients regarding the efficacy and appropriate use of vitamin supplementation.

3. Establish protocols to evaluate and monitor vitamin and nutritional needs of hospitalized and long-term care patients.

Audience Engagement System
Addressing nutrition in practice.

“Farmacy”

Poll Question 1

According to the NHANES, which is the most common nutritional deficiency in the country today?

A. Potassium       D. Vitamin D
B. Magnesium       E. Vitamin B-12
C. Zinc            F. Fiber
Common Nutrient Deficiencies

- Potassium – 98%
- Magnesium – Gen Pop 48% -- Older 83%  Older AA 90.6%
- Zinc
- Vitamin D
- Vitamin B-12
- Fiber – 95%

Potassium deficiency

- Causes
  - Low serum levels -- Medications or endocrine/adrenal
  - Chronic low intake
- Chronic deficiency – 98% do not get the RDA
  - HTN
Poll Question 2

Which of the foods listed below has the greatest amount of potassium per serving? (USDA Nutrient Database)

A. White Beans - 1 cup
B. Sun Dried Tomato – 1 cup
C. Russet Potato - 3 to 4-1/4”
D. Raisins packed– 1 cup
E. Banana mashed– 1 cup

Which of the foods listed below has the greatest amount of potassium per serving? (USDA Nutrient Database)

https://ndb.nal.usda.gov/ndb/search/list?home=true

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Mg of Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Beans</td>
<td>1 cup</td>
<td>3315 mg</td>
</tr>
<tr>
<td>Sun Dried Tomato</td>
<td>1 cup</td>
<td>1839 mg</td>
</tr>
<tr>
<td>Russet Potato</td>
<td>3 to 4-1/4” diameter</td>
<td>1644 mg</td>
</tr>
<tr>
<td>Raisins</td>
<td>1 cup</td>
<td>1361 mg</td>
</tr>
<tr>
<td>Banana</td>
<td>1 cup mashed</td>
<td>806 mg</td>
</tr>
</tbody>
</table>
Magnesium

• 4th most common mineral in the body
• EAR (estimated average requirement) 50% of adults deficient
• Subclinical deficiencies in “normal range” – Serum plus urine secretion
• Animal, epidemiologic, and clinical studies indicate: pathologic role for magnesium deficiency:
  • electrolyte, neurologic, musculoskeletal, and inflammatory disorders;
  • osteoporosis, hypertension, cardiovascular diseases, metabolic syndrome; and diabetes.


Poll Question 3

Which of the foods listed below has the greatest amount of magnesium per serving? (USDA Nutrient Database)

A. Pumpkin/squash seeds - 1 cup
B. Spinach – 1 Cup
C. Wild Coho Salmon – 3 ounces
D. New Zealand lamb – 1 ounce
E. Oatmeal cookie 1 ounce
F. Wheat Bread – 1 slice
Magnesium: USDA Nutrient Database

- EAR (Estimated Average Requirement)
  - Adult male > 18  330-350 mg/day
  - Adult female >18 255-265 mg/day

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size</th>
<th>Magnesium in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pumpkin/Squash seeds roasted and salted</td>
<td>1 cup</td>
<td>649</td>
</tr>
<tr>
<td>Spinach</td>
<td>1 Cup</td>
<td>131</td>
</tr>
<tr>
<td>Wild Coho Salmon</td>
<td>3 ounces</td>
<td>32</td>
</tr>
<tr>
<td>New Zealand Lamp</td>
<td>1 ounce</td>
<td>5</td>
</tr>
<tr>
<td>Oatmeal Cookie</td>
<td>1 ounce</td>
<td>5</td>
</tr>
<tr>
<td>Wheat Bread</td>
<td>1 slice</td>
<td>12</td>
</tr>
</tbody>
</table>

Case Study

- 64 y/o AA with obesity, DM2, hyperlipidemia, HTN, menopause, mild neuropathy
- OBTW: Hair loss noted for 3-4 years – breaking off at ¾” – some scalp pruritis rx with coconut oil. Recently worse spreading posteriorly. Braiding hair to cover thinning on top
- Meds, Pravastatin, Amlodipine, Glimepiride, not tolerate Metformin (Diarrhea), topical estrogen
- FH: no male pattern baldness
- EXAM: scalp normal skin. Diffuse thinning top and few short hairs. Pull test without exclamation point strands
• Potential Causes: Major Illness, iron deficiency, hypothyroid, heavy metal toxicity, female pattern baldness, Central Centrifugal Citcatrical alopecia

• Labs:
  • A1C 6.7%
  • HBG 11.4 g/dl
  • TSH 1.09 mIU/L
  • Vit B-12 1428 pg/ml
  • MMA < 50nmol/L
  • Arsenic, Lead, Mercury - low

Zinc

• Nearly 100 different enzymes in all 6 classes
• Some gene regulation (Ex: metallothionein)
• Small bowel absorption – albumin bound
• Coarse control – absorption
• Fine control – endogenous release
• 10-15 μmol/l serum – 0.1% of total
Zinc

• Excretion - Mostly stool, 10% urine

• Low:
  • Impaired growth velocity
  • Pregnancy outcome – (prematurity with < 6mg/dy)
  • Immune system (colds)

• “Clinically important features of zinc deficiency can occur with only modest degrees of dietary zinc restriction while circulating zinc concentrations are indistinguishable from normal.” IOM

Zinc

• Zinc deficiency in the oxidative stress control, immune response, proliferation,

• Pathophysiology of disease-
  • depression, cardiovascular diseases, diabetes mellitus, Alzheimer’s disease, and Wilson’s disease.

Zinc Absorption

- Iron – decreases absorption
- Calcium phosphate- decreases absorption but not high calcium diet
- Copper – Zinc protects in Wilson’s
- Protein – increase absorbability – Breast>cow milk
- Phytate – unleavened bread in mid east - decreases
- High fiber – no effect
- Avoid Zinc Picolinate supplement– increased urinary loss & decreased balance

Zinc Deficiency

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair loss – alopecia</td>
<td>Low Alk Phosphatase</td>
</tr>
<tr>
<td>Decreased taste</td>
<td>Low RBC/WBC Zn</td>
</tr>
<tr>
<td>Dermatitis: acne, seborrheic dermatitis, eczema</td>
<td>High Copper</td>
</tr>
<tr>
<td>Frequent infections</td>
<td>Low Vit A/beta carotene ratio</td>
</tr>
<tr>
<td>Glossitis, apthous ulcers</td>
<td>Plasma zinc responds to supplementation</td>
</tr>
<tr>
<td>Nail dystrophy – white spots</td>
<td></td>
</tr>
</tbody>
</table>
Vitamin D – 25 OH cholecalciferol

Cholesterol

7 dehydroxycholesterol

cholecalciferol

UV-B 290-315 nm

Sun Energy
VITAL –

• RCT 25,871 (5106 black)
• 2000 IU Vit D vs placebo
• 5.3 years median follow-up
• Men >50 yrs
• Women > 55 years
• 65% had blood samples before and 1 yr
• Baseline: <20ng/ml – 12.7%
  • 20-<30 ng/ml – 32.2%
• Mean -29.8 ng/ml to 41.8 ng/ml (a 40% increase)

• Primary endpoints –
  • Invasive Cancer Dx - Any
  • Major Cardiovascular – MI, CVA, Death
• Secondary
  • Types of cancer
  • Death from cancer
  • Major cardiovascular plus revascularization


VITAL Observations and Results

• At 5 years, the prevalence of outside use of vitamin D (>800 IU per day) was 6.4% in supplement and 10.8% in placebo groups
• No difference in cancer (HR 0.83; 95% CI, 0.67 to 1.02 or cardiovascular (HR 0.97, 95% CI 0.85 to 1.12)
• Lower rate of death from cancer with vit D - excluding first 2 years. HR 0.75 [95% CI, 0.59 to 0.96]
• 2014 Meta-analysis of 4 Previous vitamin D trials testing doses of 400 to 1100 IU per day administered with or without calcium Incidence RR of 1.00 (95% CI, 0.94 Death from Cancer RR 0.88 (95% CI, 0.78 to 0.98

VITAL Observations and Results

• Limited power for site-specific cancers
• A 2-year post-intervention follow to capture latency effects
• Observational studies suggest that vitamin D may confer greater protection against death from cancer than against the initial development of clinically evident cancer
  • Strongest inverse relationships between vit D levels & colorectal cancer


Vitamin D and Survival

![Graph showing survival rates with different serum vitamin D levels](image)

Survival (%) vs Years of Follow-up for different serum vitamin D levels (8 ng/mL, 13 ng/mL, 19 ng/mL).

Archives of Internal Medicine 2008;168:1340-1349
Deficiency in Healthcare Professionals – (Canada)

Rates of vitamin D deficiency among healthcare professionals were:
- healthcare students 72%
- medical residents 65%
- practicing physicians 46%
- healthcare employees 44%
- nurses 43%

Vitamin D deficiency or insufficiency (25-(OH)D < 75 nmol/L - < 30 ng/ml)


Hypertension in Blacks

- 283 Blacks, Mean age of 51 yrs - Winter Months
- 4 arm, double blind randomized trial
- Baseline, 3 month, BP & vit D
- 1.4 mmHg drop for every 1000 IU/dy (p=0.04)
- No Diastolic effects

RCT\textsubscript{DB/Placebo} Influenza A and Asthma - 1200 IU/dy


B-12 the Structure

Wickimedia Commons
Poll Question 4

Who is at greatest risk of vitamin B-12 deficiency?
A. Hindu recently moved from India to London
B. Individual with DM-2 & treated with Metformin
C. Hospitalized elderly (>65 yrs)
D. Obese middle aged male with Severe GERD on combination H2 blockers for 5 years

Answer – All are at risk – We don’t know which has the greatest risk

A. Hindu who moved from India to London
B. Individual with DM-2 & treated with Metformin
C. Hospitalized elderly (>65 yrs)
D. Obese middle aged male with severe GERD on H2 blocker & PPI for 5 years
Vitamin B-12
• Source – Cyanocobalamine, Methylcobalamin,

• Absorption
  • Salivary R-factor
  • Intrinsic Factor
  • Meat < Fortified cereals < Milk/diary < Supplements
  • Also Passive absorption in small intestine

• Actions
  • Methyl management
  • Anemia and Neuropathy
  • Recycling Homocysteine

Vitamin B-12 Deficiency

• Diagnosis
  • Symptoms
  • Macrocytic Anemia
  • Blood tests
    • Vitamin B-12 level; Methylmalonate and Homocysteine;
      Holotranscobalamin and Holohaptocorrin

• Prevalence
  • Up to 15% of population > 65 yr/old
Framingham B-12 Experience

Vit B-12 Deficient %
- <148 pmol/L  8%
- < 185 pmol/L  16%
- < 258 pmol/L  29%

- No difference with age
- Correlated with intake


“Functional Cobalamin Deficiency”

Elevations in methylmalonate > Homocysteine
- Age ≥70 years
- After exercise, folate excess
- Inflammation: DM, Tobacco, CRF, Cancers, neurodegenerative disorders, chronic infection, rheumatologic dz, asthma, pregnancy, IBD, iron overload, hyperthyroidism, cirrhosis, unexplained high ESR.

*Solomon, LR. Functional cobalamin (vit B12) deficiency: role of advanced age and disorders associated with increased oxidative stress. European Journal of Clinical Nutrition 2015 (Jan 7), 1-6.*
## Spec Sheet

**ENGINE**
- Engine type: SKYACTIV®-G1 2.0L DOHC 16-valve 4-cylinder with VVT
- Horsepower: 181 hp @ 7000 rpm
- Torque: 151 lb-ft @ 4000 rpm
- Redline: 7500 rpm
- Displacement (cc): 1998
- Bore x stroke (mm): 83.5 x 91.2
- Compression ratio: 13 : 1
- Chain-driven dual overhead cams, 4 valves per cylinder with variable intake valve timing (VVT)
- Engine block: Aluminum alloy
- Cylinder head: Aluminum alloy
- Emission Control (50 State emissions): DRIVETRAIN
- Type: Front-midship engine, rear-wheel drive
- Manual transmission

**SKYACTIV®-MT17 6-speed manual transmission with short-throw shifter**
- Automatic transmission: 6-speed Sport automatic transmission with paddle shifters

**GEAR RATIOS (:1) 6 MT**
- 1st: 5.087
- 2nd: 2.991
- 3rd: 2.035
- 4th: 1.594
- 5th: 1.286
- 6th: 1.000
- Reverse: 4.696
- Final Drive: 2.866

**CHASSIS**
- Chassis: Monocoque unibody with backbone frame construction and front and rear suspension subframes
- Brakes: 4-wheel disc
  - Front: 11-inch vented disc with single piston calipers
  - Rear: 11-inch solid disc with single piston calipers
- ABS: 4-wheel, 4-channel with overall steering ratio 15.5:1
- Steering wheel turns, lock-to-lock: 2.7
- Turning circle diameter, curb-to-curb (ft): 30.8
- Suspension: 4-wheel independent
  - Front: Double wishbone with aluminum control arms and monotube dampers
  - Rear: Multi-link with aluminum bearing support and monotube dampers

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**Mazda MX-5 -- World’s Best Selling Sports Car**

![Mazda MX-5](image)
Complexity

• The number of chemical entities in food that participates in nutritional function is infinitely large and mostly unknowable, yet highly integrated and managed.


Questions?

• Does the nutrient Dose effects cellular function?
• Does a pill form work like a food form?
• One nutrient effected by others?
• Can we measure or predict nutrient-nutrient interactions?
• Does the storage form predict active form’s function?
• How active is homeostasis at the tissue level?

Reductionism vs Eating Pattern

“Value Added”

Increased cost, increased profit, Increased Pleasure/Addiction potential

Practice Recommendations

• Encourage the intake of more minimally processed whole plants – Legumes, etc. – Healthy eating patterns
• Look for the signs/symptoms of zinc deficiency and supplement when deficiency is suspected.
• Test for vitamin B-12 deficiency (including MMA) in at risk individuals.
• Supplement in situations that are supported by evidence
Contact Information

• George E Guthrie MD MPH CDE FAAFP FACLM
• gguthrie54@mac.com

Questions
Resources/Supplemental Material


• Keum N, Giovannucci E. Vitamin D supplements and cancer incidence and mortality: a meta-analysis. Br J Cancer 2014;111:976-80.