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PENS 2015 National Conference



Type 2 Diabetes in Youth
AAP Guidelines


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Conflict of Interest Disclosure

Conflicts of Interest

- Daichi Sankyo Research grant
- Novo Nordisk Research grant

A conflict of interest exists when an individual is in a position to profit directly or indirectly through application of authority, influence, or knowledge in relation to the affairs of PENS. A conflict of interest also exists if a relative benefits or when the organization is adversely affected in any way.



Objectives

- Know how to differentiate type 1 from type 2 diabetes
- Understand glucose management: when to start insulin vs oral agents
- Know when to screen and how to manage the co-morbidities seen with type 2 diabetes in youth

SEARCH Data in Youth <20 Years

- T1DM: 15,000 youth diagnosed annually
 - Caucasians: 80% T1DM
- T2DM: 3700 youth diagnosed annually
 - Native Americans: 80% T2DM
 - Asian Pacific Islanders 70%
 - African-Americans 58%
 - Hispanics 46%

Search for Diabetes Study Group

Objectives

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- 3. To know when to screen and how to manage the co-morbidities seen with type 2 diabetes in youth

Case #1 Sarah

- Sarah is a 13 year old female who is seen for a school physical examination. Her only complaints were frequent urination of 3 weeks duration and having to get up at night to urinate. She has had no weight loss but has been feeling more tired than usual lately, which she attributes to late nights studying.
- She has a strong family history of type 2 diabetes in her mother and maternal grandfather

Physical Examination

Height was 5 ft 2 ins and weight 187 lbs.

BMI was 34.2 kg/m²

BP 128/72

Acanthosis not present on her neck

All else normal except for vaginal discharge of cottage cheese consistency

POCT Laboratory Evaluation

- HbA1c 13.2%
- Urinalysis revealed
 - 4+ glucose
 - Moderate ketonuria

What type of diabetes does this girl have?

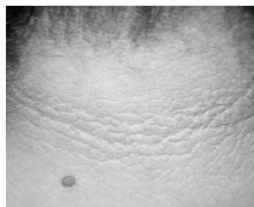
What type of diabetes does Sarah have?

- Type 1
- Type 2
- MODY
- Unsure

Type 1	Type 2
Not usually overweight Proportionate to obesity in general population	85% are overweight
Short course	Indolent Course
35-40% present with ketoacidosis	33% with ketonuria 5-25% may have ketoacidosis
5% with a 1 st or 2 nd degree relative with type 1	74-100% with 1 st or 2 nd degree relative with T2DM
Increased incidence of other autoimmune d/o: thyroid; adrenal; vitiligo; celiac	Increased incidence of metabolic syndrome: PCOS, AN (up to 90%), HTN, lipids
Decreased C-peptide & Insulin No increase with glu challenge after 1 year	NI or increased C-P & Insulin Increase with glucose challenge after 1 year
Caucasians predominate	NA; AA; Latino; Asian; Pacific Islander

Clinical Evaluation

- History
 - Family History
 - Ethnicity
 - African Americans, Mexican, Hispanics, American Indians
- Physical Examination
 - Acanthosis nigricans
 - Blood Pressure
- Laboratory Evaluation
 - Islet autoantibodies
 - ICA, IAA, GAD, IA-2, ZnT8
 - C-Peptide / insulin levels
 - after 1st year
 - Lipid profile



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Treatment Goals

- ❖ Weight reduction
 - ❖ decreases insulin resistance
- ❖ Normoglycemia and normal HbA1c
 - ❖ decreases microvascular disease
- ❖ *Control co-morbidities of insulin resistance, the most important contributors to macrovascular disease*
 - ❖ Hypertension
 - ❖ Dyslipidemia
 - ❖ Acanthosis
 - ❖ Hyperandrogenism: PCOS and hirsutism

Barriers to Adherence: Adolescent Psychosocial Issues

- DM is associated with depression and eating disorders
- - Binge eating associated with increased weight gain and high rate of depression
(TODAY, Diabetes Care, June 2013)
- Desire for peer acceptance
 - Doesn't want to be different; wants to be "cool"
 - Stressful time of life: Stress is related to poor adherence and worsened metabolic control
- Rebellion against authority
 - Listens to peers more than to parents or other adults
 - Resentment about "nagging"
 - Wants independence
 - Parenting issues are key: punitive, supportive, too permissive, too controlling
- Risk taking behaviors
 - Feels invulnerable
 - Driving, Sex, Drugs, Alcohol, Smoking



Case 2 Johnny

- Johnny is seen for a sports physical examination. He is overweight and is trying to increase activity to help him lose weight. He is asymptomatic with no symptoms of polyuria or polydipsia. He has a strong family history of type 2 diabetes.

Physical Examination/ POCT Labs

- BMI > 95% for age, gender, and height
- BP 134/86
- Acanthosis nigricans present on neck and axillae

POCT
Blood glucose 432 mg/dL
HbA1c 12%
Urine ketones small

What would you do as initial treatment?

- Diet and exercise alone
- Diet and exercise plus metformin
- Diet and exercise plus insulin
- Diet and exercise plus metformin and insulin

Targeted Glucose Control

- Base therapy on realistic glycemic goals
- Target both fasting and 2 hour postprandial glucose levels
- Implement step-wise approach
- Use whatever therapy necessary to achieve glycemic goals

Glycemic Targets*

Parameter	Normal	Reasonable Goals
Fasting (or Preprandial) Glucose	<100	70-130
Postprandial Glucose	<140	<180
Bedtime BG	<120	90-150
HbA 1c (DCCT Method)	<5.7%	<7.5%

Glucose values are plasma (mg/mL).

*Combined WHO recommendations and ADA guidelines.

AAP T2DM Guidelines: Initial Treatment

- Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM
 - who are ketotic or in diabetic ketoacidosis
 - who have venous or plasma blood glucose levels \geq 250 mg/dl
 - whose Hemoglobin A1c is $>$ 9 percent; or
 - in whom the distinction between Type 1 and Type 2 diabetes is unclear.

Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics* 2013;131:364-382

Initial Treatment (contd)

In all other instances, clinicians should start metformin as first-line therapy for children and adolescents at the time of diagnosis with T2DM, and initiate a lifestyle modification program including nutrition and physical activity.

Initial Treatment of Blood Glucose

Symptoms	Blood Glucose	Ketones	Treatment
No	<250	Negative	Metformin
No	>250	Negative	Insulin ± Oral agents
Yes	>200s	Negative	Insulin
Yes	>200s	Positive	Insulin

TODAY Study

- 699 youth with T2D followed for 3.86 years assigned to:
 - Metformin 1000 mg BID
 - Metformin + rosiglitazone 4 mg BID
 - Metformin + lifestyle intervention, incl in-person visits in addition to quarterly clinic visits
- Primary endpoint A1c <8%
- RESULTS
 - Median time to failure 11.5 months
- Failure rates:

• metformin alone	51.7%
• metformin + rosiglitazone	38.6%
- metformin + lifestyle	46.6%

Zeitler, Hirst K, Pyle L and the TODAY Study Group. N Engl J Med 2012; 366(24): 2247-2256.

TODAY Study Other Significant Findings

- Metformin + rosiglitazone more effective in girls than boys and only significantly different in girls
- Failure rates highest in African Americans:
 - 52.8% African Americans
 - 45% Hispanics
 - 36.6% Caucasians
- Metformin alone less effective in AA (66.2% fail) than in Caucasians (44.9%) or Hispanics (44.0%)
- No difference in cardiovascular risk factors (lipids, microalbuminuria, BP) among groups
- Failure rates higher in boys p 0.03:
 - 48.2% boys
 - 44.3% girls

BARIATRIC SURGERY

- Within 1 yr of surgery, RYGB improves
 - fasting insulin,
 - fasting glucose
 - HOMA-IR even though patients were still obese (average BMI 35.8 kg/m2)*
- One year follow-up of 11 T2DM adolescents who underwent RYGB:
 - 10 DCd oral hypoglycemics within 1 yr after surgery.
- The 1 patient who was insulin-dependent before surgery could not discontinue oral hypoglycemics but was
 - less insulin-resistant and
 - required lower doses of insulin.**

* Lawson ML, Kirk S, Mitchell T et al a multicenter study from the Pediatric Bariatric Study Group. J Pediatr Surg 2006;41: 137-143

Johnny and brother eating after school snack



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AAP Monitoring Guidelines Blood Glucose

- Clinicians should advise patients to monitor finger-stick BG levels in those who:
 - are taking insulin or other medications with a risk of hypoglycemia;
or
 - are initiating or changing their diabetes treatment regimen;
or
 - have not met treatment goals;
or
 - have intercurrent illnesses.

AAP Monitoring Guidelines: HbA1c

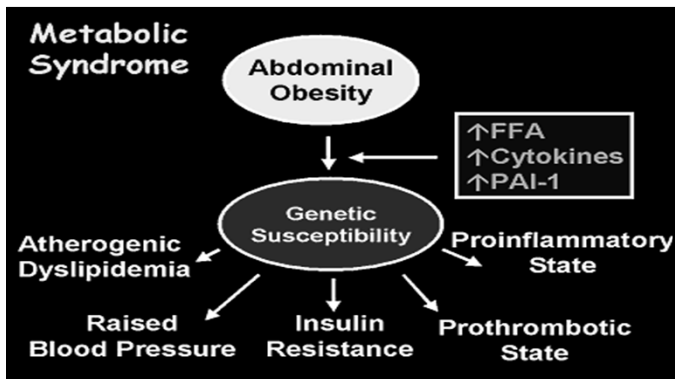
- Clinicians should monitor Hemoglobin A1c (A1c) levels every three months
- Intensify treatment if treatment goals for BG and A1c levels are not being met.

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Case 3 Corey

- Corey was diagnosed with type 2 diabetes 1 month ago. He is seen for his 1 month visit.
- Question :
- With what would you treat hypertension?
 - ACE inhibitors
 - Ca channel blockers
 - Thiazide diuretics
- With what would you treat microalbuminuria?
 - ACE inhibitors
 - Ca channel blockers
 - Thiazide diuretics
- With what would you treat dyslipidemia?
 - Resins
 - Fibrates
 - Statins



**Atherosclerosis begins in childhood:
Autopsy Studies**

- Bogalusa Heart Study (BHS): 2-15 year olds
- Pathobiological Determinants of Atherosclerosis in Youth (PADY): 15-34 year olds

Raised coronary lesions in 7% BHS and 24% PADY

- ▶ Body mass index
- ▶ VLDL, LDL-C, HDL-C, triglycerides
- ▶ Blood pressure

Complications Occur Early in T2DM

Frequency Within 1.3 Years of DM Onset

- Microalbuminuria 28%
 (7% at 3 mos)
- Hypertension 36%

Mean A1c 7.3%.....thus, not due to poor BG control

Eppens MC, et al. Diabetes Care 2006;29(6):1300-1306

**Complications Occur Early:
TODAY Trial 2012**

5-7 months after diagnosis

- 34% with HTN
- 54% with hypertriglyceridemia
- 10% with high LDL-C
- 20% with microalbuminuria
- 14% with non-proliferative retinopathy

COMPLICATION RATE IN TODAY STUDY
 TODAY Study Group. Diabetes Care. June 2013; 36: 1758-1764.

	BASELINE (n=699)	12 Months (n=512)	24 months (n=404)	36 months (n=264)
LDL-C (mg/dL) mean				
≥130 or on meds (%)	4.5	8.6	9.9	10.7
TG (mg/dL) mean				
<150 (%)	79.0	77.3	77.6	76.7
≥150 or on meds (%)	21	22.7	22.4	23.3
Apo B (mg/L)	76.6	80.3	78.9	80.1 p<0.0001
hsCRP (%) >0.3	41.2	33.9	36.2	46.3 p=0.0217

CV Risk Factors in T2DM vs T1DM
SEARCH for Diabetes in Youth
 Population based study of 2096 youth 0-19 y.o.

CVD risk factors: Waist circumference >90%
 sBP or dBP >90%
 HDL-C <40 mg/dL, TG > 110 mg/dL

2 or more CV Risk Factors in: 15% T1DM
 90% T2DM

	HTN	TG	HDL-C	WC	MS
T1DM	27.24	18.1	10.05	21.26	21.4
T2DM	65.63	65.6	61.46	95.85	92.7

TREATMENT CONSIDERATIONS

- Because of the many CV risk factors associated with insulin resistance, T2DM has earlier severe complications than T1DM in childhood.
- Vascular disease may be present at diagnosis because of the insidious onset and unknown duration of diabetes preceding diagnosis
- Thus, test for complications (urine albumin, eye exam, lipids) at T2DM dx !!!

LIPIDS

Recommendations for Lipid Treatment: Basic Guidelines

- Treatment should be based on lipid values obtained after diabetes treatment initiated
- Initial treatment: diet & exercise if LDL-C >100
- Pharmacologic rx should be considered if medical nutrition therapy has failed after 3-6 months, even if chronic hyperglycemia is present
 - Medications should be instituted if LDL is > 160 mg/dl
 - Medication should be considered if LDL is 130-159 based on the child's CVD risk profile

Recommendations for Diet

- Portion Size (palm, fist)
- Avoid sugared drinks
- MyPlate
- Snacks no more than 100 cal
- No eating out of box or bag
- Wait 15 minutes before seconds- then salad



AAP Key Action Statements

- Clinicians encourage youth with T2DM to
- Engage in moderate-to-vigorous exercise for at least 60 minutes daily
 - May need to increase gradually

- Limit non-academic screen time to less than 2 hours a day.

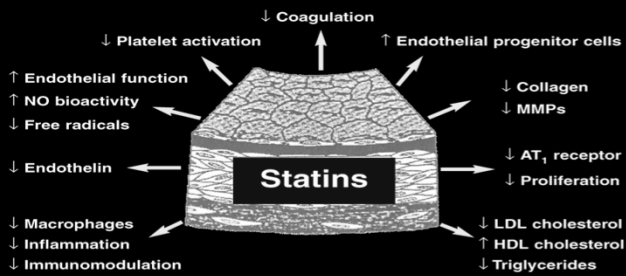


Drug Therapy

	LDL-C	HDL-C	TG
Statins	↓18-55%	↑5-15%	↓7-30%
Bile acid sequestrant	↓15-30%	↑3-5%	May increase
Fibrates	↓10-20%	↑20-30%	↓20-50%
Ezetimibe	↓18%		
Niacin	↓5-25%	↑15-35%	↓25-50%

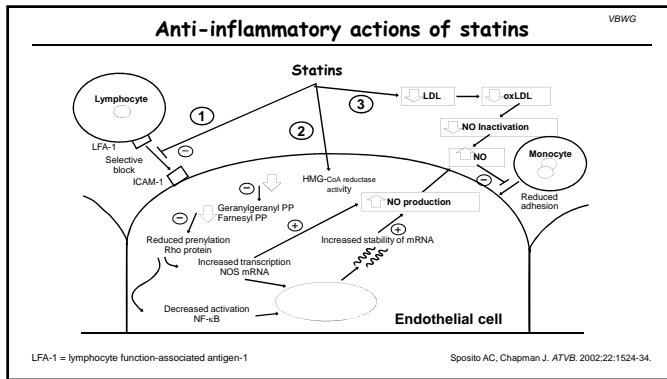
Pleiotropic effects of statins on the vessel wall

VBWG



MMPs = matrix metalloproteinases

Wassmann S, Nickenig G. *Endothelium*. 2003;10:23-33.



Statins

Concerns over statin use:

- Elevated transaminase levels
 - 0.5-2%, reversible and dose related
- Muscle symptoms (myositis, weakness, rhabdomyolysis)
 - Risk of severe myositis <0.1%
- Tolerability

Pasternak RC, et al. J Amer Coll Cardiol. 2002;40:7-572

Summary for Clinical Management of Safety Issues

- Measure baseline AST, ALT before statin use
- Can continue statins if ALT/AST are <3X upper limits of normal if monitor closely
- D/C statin if muscle symptoms appear and measure CPK
- If CPK is WNL or <3X normal, can continue statin and monitor symptoms. Consider dose reduction
- Statin must be discontinued if CPK is >10X normal

• Pasternak RC, et al. J Amer Coll Cardiol. 2002;40:7-572

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MICROALBUMINURIA & BLOOD PRESSURE

Microalbuminuria

- Normal <30 mg/gm creat on spot urine
- Represents inflammatory state of vessels
- Increased in white coat HTN and non-dippers
- Obtain 2 additional urine samples at least 1 month apart over the next 3-6 months
 - Ideally with first morning void
- If all 3 abnormal, treat with ACE-I

Hypertension and T2DM

- DM and glucose intolerance double risk of HTN
- Cause of HTN is multifactorial
 - Volume expansion
 - Stiff vessels
 - Decreased NO mediated vasodilatation
 - Increased angiotensin activity

BP Treatment

- Initial treatment: dietary (limit salt) and lifestyle interventions for weight reduction & exercise
- If BP doesn't reach target of $\leq 95\%$ for age, gender, height within 3-6 months, treatment with anti-hypertensive agent should be initiated
- ACE-I is rx of choice
 - Anti-hypertensive
 - Anti-thrombotic: inhibits platelet aggregation & endothelin
 - Vasodilation: \downarrow production of angiotensin II ; \uparrow bradykinin levels
 - Limits smooth muscle proliferation & plaque rupture
 - Slows progression of nephropathy & retinopathy
- If AER > 30 mg/d, > 20 mg/min, or > 30 mg/gm creatinine, strive to maintain BP $\leq 120/75$
 - Dose titrated to maintain BP $< 90\%$
 - Consider adding meds if goals not reached with ACE alone

We do a Poor Job of Treating HTN and hyperlipidemia: SEARCH Study Preliminary Results

- Lipid levels were measured in 2843 children with overweight
 - 19% had Total cholesterol ≥ 200 mg/dl
 - 14% had LDL-C ≥ 130 mg/dl
 - 7% had TG ≥ 200 mg/dl
- 1% on lipid lowering meds
- 4% on metformin
