Pediatric Endocrinology
Family Medicine Refresher Course

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I have no conflict of interests
• Short stature
• Abnormal Puberty
  – Precocious Puberty
  – Delayed Puberty
• Diabetes
  – Type 1 Diabetes
  – Type 2 Diabetes
Short Stature
Definitions

• Short Stature: height more than 2 standard deviations below mean for age
  – <3rd percentile

• Mid parental height
  – Girls [(Father’s ht – 5in)+ Mother’s ht]/2
  – Boys [(Mother’s ht + 5in)+ Father’s ht]/2

• Target height
  – MPH +/- 2 SD (1 SD = 2 inches)
Normal Growth

• Normal growth rate is age and pubertal status specific
• Age
  – 0-6 months: 1 inch per month
  – 7-12 months: ½ inch per month
  – 12-24 months: >4 inches per year
  – 24-36 months: 3 inches per year
  – 36-48 months: 2.75 cm per year
  – 4-10 years: 2-2.4 inches per year
Growth Measurement

Measure 3 times (should have <0.3 cm variation) and take mean

• Age <2 years
  – Supine length
  – Firm board with fixed head plate and moveable foot plate

• Age >2 years
  – Wall mounted stadiometer
  – No shoes, hair down
  – Head, thoracic spine, buttocks and heels should be touching the vertical surface
• Growth velocity provides the earliest identification of problems with growth.
• Growth velocity is best assessed using measurements taken at 3- to 4-monthly intervals in infants and at 6-monthly intervals in older children.
• An appropriate growth chart is an essential tool for the screening, surveillance and monitoring of children's growth.
Red Flags

- Abnormal growth velocity
- Crossing percentile curves (after 18 months)
- Height below 3rd percentile
- Significantly short for family
- Weight loss
- Excessive weight gain
A) Proportionate Short Stature

1) Normal Variants:
   i) Familial
   ii) Constitutional Growth Delay

2) Prenatal Causes:
   i) Intra-uterine Growth Restriction-
      Placental causes, Maternal nutrition, Teratogens
   ii) Intra-uterine Infections
   iii) Genetic Disorders (Chromosomal & Metabolic Disorders)
3) Postnatal Causes:
   i) Undernutrition
   ii) Chronic Systemic Illness
       - Cardiopulmonary: CHD, Chronic Asthma, Cystic Fibrosis
       - Renal: RTA, CRF, Steroid dependent Nephrotic Syndrome
       - GI and Hepatic: Malabsorption, IBD, chronic liver disease
       - Chronic Severe Infections
       - Hematological: Thalassemia, Sickle cell disease, anemia
iii) Psychosocial Short Stature (emotional deprivation)

iv) Endocrine Causes:
   - Growth Hormone Deficiency/insensitivity
   - Hypothyroidism
   - Juvenile Diabetes Mellitus
   - Cushing Syndrome
   - Pseudohypoparathyroidism
   - Precocious/delayed puberty
B) Disproportionate Short Stature

1) With Short Limbs:
   - Achondroplasia, Hypochondroplasia, Chondrodysplasia punctata, Chondroectodermal Dysplasia, Diastrophic dysplasia, Metaphyseal Chondrodysplasia
   - Deformities due to Osteogenesis Imperfecta, Refractory Rickets

2) With Short Trunk:
   - Spondyloepiphyseal dysplasia, Mucolipidosis, Mucopolysaccharidosis
   - Caries Spine, Hemivertebrae
Work Up

- Thorough history including personal and family health history, pubertal history
- Review of Growth Chart
- Exam, including height and proportion measurements
- Initial: CBC, UA, Electrolytes, T4/TSH, ESR
- Bone Age
- Specialized: IGF-1, IGFBP3, Karyotype (girls), stool studies, ? Sweat Chloride test
Familial Short Stature

- Attain the appropriate %
- Normal linear growth, parallel to the curve
Constitutional Delay

- Growth slows in 1st 2 years
- Skeletal maturation, puberty delayed
- Final height appropriate
Endo Causes

- Abnormal growth velocity
- Failure to maintain height %
IGF and IGFBP

- GH (anterior pituitary)
  - Pulsatile
  - Regulated by GHRH and somatostatin
- IGF-1 – stimulated by GH
- IGFBP – correlated with GH secretion
Growth Hormone

• FDA indications:
  – Growth Hormone Deficiency (1985)
  – Chronic Renal Failure (1993)
  – Turner Syndrome (1997)
  – Prader-Willi Syndrome (2000)
  – Small for gestational age (2001)
  – Noonan syndrome (2007)
Effect of Growth Hormone

- GH dose of 0.15 – 0.3 mg/kg/week
  - SQ, 6-7 once daily doses
- Side effects (uncommon) – Pseudotumor cerebri, SCFE
- In GH deficiency: Treatment outcome depends on duration and dose
  - First year: 9-10 cm
  - Next 2 years: 5-6 cm/year
- In ISS: Overall height gain of 3.5-7.5 cm
Puberty
Definitions

- **Puberty**: developmental stage child → young adult
  - maturation of gametogenesis
  - secretion of gonadal hormones
  - secondary sexual characteristics
  - reproductive functions.

- **Thelarche**: onset of breast development, an estrogen effect.
- **Pubarche**: onset of sexual hair growth, an androgen effect
- **Menarche**: onset of menses
- **Spermarche**: appearance of spermatozoa in seminal fluid.
- **Adrenarche**: refers to the onset of the adrenal androgen production that contributes to pubarche.
Onset of Puberty

- #1 determinant: genetics, ethnicity
- Other factors: hormonally active environmental chemicals, nutrition, general health

**Girls:** Breast buds 8-13 y

**Boys:** Testicular enlargement 9-14 y
SMR Girls

- Menses
- Growth spurt

Stage 1: Pubic hair
Stage 2
Stage 3
Stage 4
Stage 5
SMR Boys

- Prepubertal
- Enlargement of scrotum and testis
- Enlargement of penis in length
- Development of Glans, enlargement of penis width
- Adult Genitalia

Growth spurt
Abnormal Puberty

Signs of puberty before the age of 8y

- No breast development by the age of 13y
- No menarche at 15y → primary amenorrhea

OR

Signs of puberty before the age of 9y

- No testicular enlargement by the age of 14y
Questions for PCP

- History and Exam (tanner stage - SMR)
  - Is pubertal development really occurring outside the normal temporal range?
  - What is the underlying mechanism, is it associated with a risk of a serious condition?
  - If puberty progresses, would this impair the child’s normal physical and psychosocial development?
Concern for Precocious puberty

**Normal**
- Age > 8 years
- Progression over 2-5 y
- Familial Ethnicity
- Minipuberty of Infancy

**Premature Adrenarche**
- NO breasts or Testes
- Elevated Adrenal Androgens
- Idiopathic Benign Premature Adrenarche (#1), Late Onset CAH, Androgen secreting tumors

**“True” Precocious Puberty**
- BREASTS or TESTES

**Central (gonadotropin)**
- High LH and FSH (stim test)
- Advanced BA
- Idiopathic (#1), CNS lesions

**Peripheral**
- Normal LH and FSH, High E or T.
- Advanced BA
- Tumors (ovarian, testicular, adrenal). MCCunne Albrights. Testotoxicosis. Exposures
### Table 2. Etiologies of Precocious Puberty

<table>
<thead>
<tr>
<th>GnRH-Dependent Females and Males</th>
<th>GnRH-Independent Females</th>
<th>GnRH-Independent Males</th>
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</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>MAS</td>
<td>FMPP</td>
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<tr>
<td>International adoption</td>
<td>Estrogen-secreting ovarian tumor</td>
<td>Leydig cell tumor</td>
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<tr>
<td>Acquired CNS insults</td>
<td>Ovarian cyst</td>
<td>Human chorionic gonadotropin-secretin tumor</td>
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<tr>
<td>Brain tumor [astrocytoma, pineal tumor, optic pathway glioma (NF1), craniopharyngioma (rare)]</td>
<td>Estrogen-secreting adrenal tumor</td>
<td>Androgen-secreting adrenal tumor</td>
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<tr>
<td>Cerebral palsy</td>
<td>Exogenous estrogen exposure</td>
<td>Exogenous T exposure</td>
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<tr>
<td>Hydrocephalus</td>
<td>Peutz-Jegher syndrome</td>
<td>Congenital adrenal hyperplasia</td>
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<tr>
<td>CNS irradiation</td>
<td>Primary hypothyroidism</td>
<td>Primary hypothyroidism</td>
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<tr>
<td>CNS trauma</td>
<td>Aromatase excess</td>
<td>(testicular enlargement only)</td>
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<tr>
<td>CNS infection</td>
<td></td>
<td>Familial glucocorticoid resistance</td>
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<tr>
<td>CNS granulomatous disease</td>
<td></td>
<td>MAS (rare)</td>
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<tr>
<td>Subarachnoid cyst</td>
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<td>Hypothalamic hamartoma</td>
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<td>Neurofibromatosis, type 1</td>
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<td>Tuberous sclerosis</td>
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<td>Sturge-Weber syndrome</td>
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<tr>
<td>Withdrawal of chronic sex hormone exposure</td>
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<tr>
<td>Septo-optic dysplasia (rare)</td>
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<tr>
<td>Gain of function mutation of kisspeptin/kisspeptin receptor</td>
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</tbody>
</table>
Evaluation

**HISTORY**
- Age of onset
- First sign/symptom
- Other signs/symptoms
  - Breast/testes
  - Vaginal discharge
  - Erections
  - Acne, Facial hair, Body odor
  - Growth spurt
  - CNS symptoms
- Rate of Progression
- Past medical history
- Family History
  - Age of menarche, end of growth spurt, Mid parental height

**PHYSICAL EXAM**
- Growth chart
  - Growth velocity
- Tanner Staging
- Skin
  - Birth marks
  - Acne, facial hair
  - Acanthosis, striae
- Neuro exam – cranial nerves

**WORK-UP**
- Hormone measurements
  - Gonadotropins: LH, FSH
  - Gonads: Estradiol, Testosterone
  - Adrenals: 17 OHP, DHEA-S, Androstenedione
  - Metabolic Syndrome (?)
  - Bone Age
  - Other (?)
    - Brain MRI
    - Pelvic US
    - Testicular US
Treatment : CPP

- CPP: GnRH agonist administration results in an initial transient stimulation of gonadotropin secretion from the pituitary, followed by a complete, but reversible, suppression of the pituitary-gonadal axis
  - Depot Lupron 7.5 mg every 28 days or 11.25 mg every 28 days or 15 mg every 28 days
  - Depot Lupron 11.25 mg every 3 months or 30 mg every 3 months
  - Histrelin Implant upto 1 year
• Peripheral Precocious Puberty: Does not respond to GnRH agonist therapy. Instead, treatment is directed at removing or blocking the production of and/or response to the excess sex steroids, depending on the cause:
  – Tumors of the testis, adrenal gland, or ovary – These are treated by surgery. hCG-secreting tumors may also require radiation therapy and chemotherapy, depending upon the site and histologic type.
  – Functioning follicular cysts of the ovary – These develop and regress spontaneously, so conservative management without surgery is generally appropriate
  – Exposure to exogenous sex steroids – The source should be identified and removed. After removal, the pubertal changes are likely to regress.
Concerns for Delayed puberty

**Constitutional**
- + Family history. Variant of normal?

**Gonadotropin Deficiency**
- LOW LH and FSH
  - CNS Lesions
  - Chronic Illness
  - Low BMI
  - Kallmann

**Gonadal Failure**
- HIGH LH and FSH
  - Turner
  - Klinefelter
  - DSD’s
  - Radiation
  - ChemoTx
  - Autoimmune surgical

**DSD’s**
- Radiation
- ChemoTx
- Autoimmune surgical

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**Table 1. Frequency and Common Causes of Delayed Puberty Other Than Constitutional Delay of Growth and Puberty.**

<table>
<thead>
<tr>
<th>Delayed Puberty</th>
<th>Hypergonadotropic Hypogonadism</th>
<th>Permanent Hypogonadotropic Hypogonadism</th>
<th>Functional Hypogonadotropic Hypogonadism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td></td>
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<tr>
<td>Boys</td>
<td>5–10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Girls</td>
<td>25</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Common causes</td>
<td>Turner’s syndrome, gonadal dysgenesis, chemotherapy or radiation therapy</td>
<td>Tumors or infiltrative diseases of the central nervous system, GnRH deficiency (isolated hypogonadotropic hypogonadism, Kallmann’s syndrome), combined pituitary-hormone deficiency, chemotherapy or radiation therapy</td>
<td>Systemic illness (inflammatory bowel disease, celiac disease, anorexia nervosa or bulimia), hypothyroidism, excessive exercise</td>
</tr>
</tbody>
</table>
# Etiology: Delayed Puberty

## Girls
- Constitutional delayed puberty
- Gonadotropin deficiency
  - Functional gonadotropin deficiency
    - Anorexia nervosa
    - Excessive exercise with decreased body fat
    - Chronic illness (e.g., Crohn disease, cystic fibrosis, sickle cell anemia)
  - Isolated gonadotropin deficiency
    - Non-X-linked Kallmann syndrome
  - Multiple pituitary deficiencies
- Primary gonadal failure
  - Turner syndrome (gonadal dysgenesis)
  - Total body radiation for treating malignancies
  - Autoimmune ovarian failure

## Boys
- Constitutional delayed puberty
- Gonadotropin deficiency (hypogonadotropic hypogonadism)
  - Isolated gonadotropin deficiency
    - Kallmann syndrome (with anosmia)
      - Idiopathic
    - Functional gonadotropin deficiency due to chronic illness
  - Multiple pituitary hormone deficiencies
    - Congenital
    - Acquired due to a central nervous system lesion (such as a craniopharyngioma)
- Primary gonadal failure (hypergonadotropic hypogonadism)
  - Radiation to the testes
  - Following surgery for cryptorchidism
  - Vanishing testes syndrome
  - Klinefelter syndrome (small testes but adequate androgen production)
Evaluation

• **HISTORY**
  – Age of evaluation
  – Signs present/absent
    • Breast/testicular changes
    • Vaginal discharge/bleeding
    • Erections
    • Growth spurt
    • CNS symptoms
    • **Anosmia**
    • **Diet and Exercise**
  – Past medical history
  – Family History
    • Age of menarche, end of growth spurt
    • Mid parental height

• **PHYSICAL EXAM**
  – Growth chart
    • Growth velocity
    • **BMI**
  – Tanner Staging
  – GU exam
  – Neuro exam – cranial nerves

• **WORK-UP**
  – Labs
    • Gonadotropins: LH, FSH
    • Gonads: Estradiol, Testosterone
    • **Pituitary: growth factors, thyroid, prolactin (F)**
    • Chronic illness
  – Bone Age
  – Other (?)
    • Brain MRI
    • Pelvic US
    • Testicular US
Constitutional Delay

• "Watchful waiting" with reassurance and psychological support for the patient and family.
• Administration of gonadal steroids
• Short-term therapeutic goals include:
  – Attainment of age-appropriate secondary sex characteristics
  – Induction of a growth spurt *without* inducing premature epiphyseal closure
  – Potential induction of puberty
Diabetes
1. HbA1C ≥6.5%*.

   OR

2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

   OR

3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during a 75 g OGTT.

   OR

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

How prevalent is type 2 diabetes in children?

A. 1 in 100
B. 1 in 500
C. 1 in 1,000
D. 2 in 10,000

Correct answer: D

Although there are no good epidemiologic studies on type 2 diabetes, data from SEARCH (a clinic-based observational study) suggest that the prevalence of diagnosed type 2 diabetes is about 2 per 10,000 children.
Epidemiology of Diabetes

• T1D is the most common form of diabetes in children (80% of all pediatric diabetes)
  – 1 in 300-500

• T2D Ethnicity- and race-specific prevalence are:
  – Non-Hispanic whites: 1.9 per 10,000
  – Hispanics: 4.8 per 10,000
  – Asian Americans: 5.4 per 10,000
  – African Americans: 10.5 per 10,000

Epidemiology of T1D

- **Incidence in the US**
  - 27 new cases per year per 100,000 population
  - Increasing since the 1960’s

- **Age at diagnosis**
  - From 6 months to adulthood
  - Incidence peaks at age 12 (10-14) years

- **Race/ethnicity**
  - All races/ethnicities but most common in non-Hispanic Whites
Eisenbarth Model of Stages in T1D Development

Modified from G.S. Eisenbarth NEJM 1986
• Type 1 diabetes:
  – absolute deficiency of insulin (often autoimmune)

• Type 2 diabetes:
  – insulin resistance with a relative insulin deficiency
<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity/race</td>
<td>European-Americans</td>
<td>Native Americans Hispanics Hispanic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Americans Asians</td>
</tr>
<tr>
<td>Family history of diabetes mellitus</td>
<td>Rare</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Not seen</td>
<td>Common</td>
</tr>
<tr>
<td>Overweight</td>
<td>Less common</td>
<td>100%</td>
</tr>
<tr>
<td>Diabetic ketoacidosis at diagnosis</td>
<td>&gt;50%</td>
<td>&lt;&lt;50%</td>
</tr>
<tr>
<td>C-peptide (associated with insulin production) or insulin</td>
<td>Low or undetectable</td>
<td>High or normal</td>
</tr>
<tr>
<td>Antibodies associated with type 1 diabetes: GAD 65, IA2</td>
<td>Usually positive</td>
<td>Usually negative</td>
</tr>
</tbody>
</table>
• In otherwise ‘typical’ T2D, diabetes autoantibody testing should be considered because of high frequency of islet cell autoimmunity
  – Pre-pubertal children are unlikely to have T2D even if obese
  – Antibodies with high C-peptide
    • *support* the diagnosis of T1D caught before insulin absolute insulin deficiency OR
    • “Type 2 DM” who will require insulin for glucose control more quickly
Symptoms and Signs

**Symptoms:**
- 3 Polys:
  - Increased thirst*
  - Increased urination*
  - Increased appetite
- Weight loss
- Nausea
- Vomiting
- Abdominal pain*
- Rapid breathing*
- Fatigue
- Dehydration*
- Altered mental status

**Signs:**
- Increased HR*
- Decreased BP
- Tachypnea*
- Dry mucous membranes*
- Delayed capillary refill*
- Change in weight %’s
- Fruity odor to breath*
- Abdominal tenderness*
- Obtundation
- Coma

*Denotes signs and symptoms in DKA
Diabetic Ketoacidosis

**D** – **Diabetes** (extreme hyperglycemia : Plasma Glucose > 250 mg/dl)

**K** – **Ketones** (urine vs. serum)

**A** – **Acidosis** (pH < 7.3, HCO3 < 15)

**Cerebral edema** - most common fatal complication of DKA

- Risk Factors: young age, new diagnosis, severity of acidosis, increase BUN at presentation, use of bicarb for tx
- Neurologic deterioration → Give IV Mannitol 1g/kg (don’t wait for imaging)
Management T1D

- Family Education
- Glucose monitoring
- Nutrition/Carbohydrate counting
- Insulin
- Monitoring for complications and comorbidities
GOAL: mimic the function of the pancreas with basal and bolus insulin

- **Basal**: insulin required during fasting in order to cover glucose released by liver
- **Bolus**: insulin required to cover carbohydrates or to correct a high blood glucose
  - Carb Ratio, Correction Factor

- Ideal pediatric blood sugar range: 80-180 mg/dl
- HbA1c goal as defined by ADA: <7.5%
• Rapid acting insulin analogs
  – Lispro, Aspart, Glulisine
• Short acting
  – Regular
• Intermediate acting
  – NPH
• Long acting / Basal
  – Detemir, Glargine, Basaglar, Tresiba
Basal/bolus: 4 shot regimen

- Extra injection
- Flexibility with meals
- Improved glycemic control
- Weight gain?
Insulin Pumps: Open Loop

• What do they do?
  • Basal rate(s)
  • Food boluses
  • Correction bolus

• What don't they do?
  • User must enter BGs, carbs, etc.
MiniMed 670G: The First Hybrid Closed Loop System (FDA approved Sept 2016)

The Medtronic MiniMed 670G system is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of Type 1 diabetes mellitus in persons, fourteen years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 670G System includes SmartGuard HCL technology, which can be programmed to automatically adjust delivery of basal insulin based on Continuous Glucose Monitor sensor glucose values, and can suspend delivery of insulin when the sensor glucose value falls below or is predicted to fall below predefined threshold values.
Management T2D

- Family education
- Glucose monitoring
- Lifestyle modifications
  - Nutrition
  - Physical activity
- Pharmacotherapy
- Treatment of comorbidities and complications
Management T2D: Education

• Families of children with type 2 diabetes should be informed that some risk factors for diabetes are not modifiable (e.g., genetics), while others are modifiable (e.g., weight)

• They should also understand that physical activity and weight loss can help normalize glucose concentrations by reducing insulin resistance
Goal is to achieve an $A_1c < 7\%$
- Equivalent to fasting glucose concentration of 70-130 mg/dL and post prandial glucose concentration <180 mg/dL
Ways to lower glucose in T2D

• Decreasing insulin resistance
  – Physical Activity
  – Weight loss
  – Use of certain medicines (insulin sensitizers)

• Increasing insulin secretion
  – Drugs (not FDA approved in children)
  – Insulin
Metformin

• First-line treatment for T2D in children

• Dosing:
  – Start with a low dose (500 mg) and increasing the dose by 500 mg every 3 to 7 days. The maximum effective dose is 2,000 mg/day
  – Example:
    • Week 1: 500 mg PO with dinner
    • Week 2: 500 mg PO with breakfast and 500 mg PO with dinner
    • Week 3: 500 mg PO with breakfast and 1000 mg PO with dinner
    • Week 4: 1000 mg PO with breakfast and 1000 mg PO with dinner

• Does not cause weight gain or hypoglycemia
Thank you for your time and attention!!!
Questions?