Understanding Obesity Pathophysiology to Improve Clinical Care

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Clinical Nurse Coordinator, WOW 4 Wellness Clinic

Pediatric Obesity:

CDC Growth Charts for age & gender

- Underweight: < 5thile
- Healthy Weight: 5-84thile
- Overweight: 85-94thile
- Obesity: 95-99thile
- Severe Obesity: > 99thile


Obesity further defined:

- Class I obesity
  - (200% percentile to <120% of the 95th percentile)
- Class II obesity (Severe obesity)
  - (120% to <140% of the 95th percentile) or a BMI ≥ 35 to < 39, whichever was lower
- Class III obesity (Severe obesity)
  - (≥140% of the 95th percentile) or BMI ≥ 40, whichever lower.

23 Million children in US have Overweight or Obesity

1 in 3 ME Kindergarteners - overweight or obesity
27.6% of ME high school students - overweight or obesity
4.5 million children in US with Severe Obesity

Severe obesity (Class II & III) is the fastest-growing subcategory of obesity in youth.

- Demands Treatment
  - Ogden, Carroll, et al. (2014) 1; Skelton, Perrin, Skelton (2016) 2; Ogden, Carroll, Fryar et al. (2015) 3

It’s a new world

Obesity: a Disease

- Is it a Disease?
- Is it solely a Behavioral Disease or a Disease of Energy Management Dysregulation?
- Understanding the pathophysiology is the path to developing and implementing meaningful and effective therapies.
- Significant research illustrates 85% of Energy regulation is at the subconscious level (munzberg et al)

Other examples of “behavioral” diseases...

- Depression: “pull yourself up by your bootstraps” now replaced with scientifically based neurobiological therapy to treat this disease disorder. Not all patients respond to the same medication – however, for many, medication is life-saving.

- Addiction: personality flaw, weakness – now we understand the genetic underpinnings and regulatory hormones that impact addiction – hedonic centers of the brain. Medications now used to target these areas are often needed.

- ADHD: “just focus” redirection — for some these interventions may be effective; most require medication to achieve their academic potential.

- Bariatric Surgery: Currently the BEST durable treatment for Severe Obesity:
  - Has provided invaluable information re: the pathophysiology of obesity.
  - Will grade development of non-surgical therapies.
Medical Complications of Obesity

236 comorbidities affecting EVERY organ system and medical specialty

The body seeks a stable fat mass
Just as other regulated tissues do
At the subconscious level via homeostatic physiologic mechanisms

Obesity: Basic Physiology & Homeostasis

POMC/CART neurons
- Orexigenic
  decreases food intake
  increases energy expenditure via (-) AgRP/NPY & (+) neurons in PVN via MC3R
  insulin and leptin receptors
- Anorexigenic
  decreases appetite and increase EE

AgRP, NPY neurons
- Orexigenic
  increases food intake
  decreases energy expenditure via (-) orexigenic neurons in LH & PVN (POMC/CART) via MC3R and MC4R
  (-) orexigenic neurons in LH and PVN via NPY
  Ghrelin receptors
Paraventricular Hypothalamus: Second order neuron

- MC4R deficiency or mutation leads to obesity
- Decreases appetite
- Increases energy expenditure via SNS stimulation

The Energy Regulatory System (ERS): Hormonal and Neural control, modulated by Environmental factors

- Hormonal Control
  - Leptin
  - Adiponectin
  - Insulin
  - Glucagon
  - Ghrelin
  - GLP-1, GIP
  - PYY
- Cortisol
- ERS
- Environmental Modulation
- Neuronal Control
  - Cognitive Brain
  - Pedestal (Primal)
  - Homeostatic (Hypothalamus)

Obesity results from a failure of normal weight and energy regulatory mechanisms...
...leading to an elevated body fat set point

Complex Biology of Obesity

Critical Periods of Development and Obesity

- Prenatal and Infancy
  - SGA/LGA
  - GDM
  - Maternal HTN, Obesity
  - Rapid growth/weight gain during infancy

- Early Childhood
  - Adiposity Rebound
  - Consider syndromic & monogenic etiologies
    - Prader-Willi syndrome, Bardet-Biedl syndrome, Alston syndrome (POMC,MC4R def)

- Adolescence
  - Impact on puberty
  - High risk to persist into adulthood
Genetics of Obesity

- 900 genetic loci spread across the genome
- Variations in the DNA sequence at these loci are associated with obesity
- Most common variations are near the melanocortin-4 receptor (MC4R) and FTO genes
- Each locus has a small effect
- People with multiple variant loci have a high risk of severe obesity (BMI > 40)

### Syndromic Obesity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Key Characteristics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prader-Willi Syndrome</td>
<td>Short stature, hypotonia, developmental delay, hyperphagia</td>
<td>[5q13 deletion on paternal chromosome; increased ghrelin levels]</td>
</tr>
<tr>
<td>Bardet-Biedl Syndrome</td>
<td>Retinitis pigmentosa, polydactyly, hypogonadism, hypotonia, developmental delay</td>
<td>Autosomal recessive; Defect in cilia</td>
</tr>
<tr>
<td>Albright Hereditary Osteodystrophy</td>
<td>Developmental delay, short stature, and short fourth and fifth metacarpals, hypogonadism</td>
<td>Developmental delay, short stature, and short fourth and fifth metacarpals, hypogonadism</td>
</tr>
<tr>
<td>Fragile X</td>
<td>Intellectual disability, large ears, large testes, CCG trinucleotide affecting FMR1 gene on X chromosome</td>
<td>FSH Hybridization</td>
</tr>
<tr>
<td>Cohen Syndrome</td>
<td>Obesity, hypotonia, microcephaly, prominent pinnae</td>
<td>Chromosome 2q (q22) Autosomal</td>
</tr>
<tr>
<td>Beckwith-Wiedemann Syndrome</td>
<td>Macrocephaly, macrostomia, hypoglycemia, ear pits, midline abdominal wall defects</td>
<td>Increased cancer incidence (Wilms tumor, hepatoblastoma)</td>
</tr>
<tr>
<td>Mitelman Syndrome</td>
<td>Sensory hearing loss, blindness, short stature, hypoglycemia, dilated cardiomyopathy</td>
<td>Mutation in AC053 gene</td>
</tr>
</tbody>
</table>

### Rare Genetic Disorders

- Likely underdiagnosed
- True prevalence of rare genetic disorders of obesity is unknown due to genetic testing not routinely done in patients with obesity.
- Examples:
  - LEPR: 76 individuals detailed in case studies worldwide
  - POMC: 31 individuals detailed in cases worldwide
  - PCSK1: 43 individuals in cases worldwide
  - 8500 estimated prevalence in US

### Monogenic Obesity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Leptin Deficiency</td>
<td>Early-onset severe obesity and hyperphagia, altered immune function, delayed puberty</td>
<td>Mutations in the ob gene, Undetectable serum leptin levels, Treatment with leptin</td>
</tr>
<tr>
<td>Congenital Leptin Receptor Deficiency</td>
<td>Early-onset severe obesity and hyperphagia, altered immune function, delayed puberty</td>
<td>Normal serum leptin levels</td>
</tr>
<tr>
<td>Melanocortin 4 Receptor (MC4R) Mutation</td>
<td>Tall stature and rapid growth</td>
<td>Normal mental status</td>
</tr>
<tr>
<td>Pro-opiomelanocortin (POMC) Mutation</td>
<td>Red hair, pale skin, low blood pressure or rapid pulse, and corticotropin deficiency, adrenal insufficiency</td>
<td>Hypopigmentation, and isolated ACTH deficiency</td>
</tr>
</tbody>
</table>
Stress is like “transient diabetes”

Obesity Medicine Board Review

Stress is like “transient diabetes”


Decreased Metabolic Rate and Increased Food Intake

Increased Hedonic Drive and Consumption of Palatable Foods

Stress

Increased Cortisol

Hyperinsulinemia/Insulin resistance

Leptin Resistance

Treatment Algorithm

Obesity with ADHD

Screen for Co-occurring & Associated Disorders

Screener for ADHD

Sleep Disorders

Disordered eating patterns

Mental Health Concerns

Referral of low-income

Obesity without ADHD

Screen for ADHD

Innovations

Standard Care PLUS:

- Comprehensive ADHD intervention
- Sleep hygiene, school work
- Social & community
- Diet & nutrition
- Cognitive Behavioral Therapy
- Psychotherapy
- Pharmacotherapy
- Exercise

Standard Care:

- Supportive care
- Psychotherapy

The Obesities – A Plethora of Discrete Disorders

Multiple Types of Obesity (“The Obesities”)

Multiple Subtypes = Variation in Treatment Response
Current AAP & USPSTF Recommendations

**AAP 2007 Guidelines**
- **Stages**
  - Stage 1: PCP
  - Stage 2: PCP w/monthly F/U
  - Stage 3: Multidisciplinary – with +/− Medications
  - Stage 4: Multidisciplinary – outside PCP setting, +/− Medications

**USPSTF 2017 Recommendations**
- Mod-High intensity for BMI > 85%
- Minimum of 25 hours in 6 months, up to 75 hrs in 12 months
- Must include behavioral component
- Grade B
- Covered by ACA as Preventive Service

WOW 4 Wellness: Bangor
- Weight & Wellness: Portland

WOW Structure
- Multi-phased program
  - Phase 1 Weekly X 8
  - Phase 2 Every 2 weeks X 6
  - Phase 3 Monthly X 6
  - Phase 4 Ongoing (usually every 2-6 weeks)
- Focused curriculum
  - Each visit building on previous visit
- Research
- IRB WOW
- IRB POWER (multi-institutional)
- Family focused

WOW Team
- **Dr. Valerie M. O’Hara**
  - Pediatric Obesity Specialist (ABOM)
- **Starr Johnston, RN**
- **Kathrin Hastey**
- **Melissa Bernardini, RD**
- **Jennifer Curran, PhD**
- **Laurie Overlock**
- **Personal Trainers**
- Pediatric Obesity Specialist (ABOM)
- RN, Clinical Coordinator
- FNP, Medical Provider
- Registered Dietician
- Pediatric Psychologist
- Medical Receptionist
- Community Partnerships

WOW 4 Wellness
- Multi-phased program
- Phase 1 Weekly X 8
- Phase 2 Every 2 weeks X 6
- Phase 3 Monthly X 6
- Phase 4 Ongoing (usually every 2-6 weeks)
- Focused curriculum
- Each visit building on previous visit
- Family focused

WOW Clinic Protocol
- Covered by ACA as Preventive Service
- Grandfathered policy
- No cost sharing
- WOW Clinic Protocol
- Multi-phased program
  - Phase 1 Weekly X 8
  - Initial Medical visit, initial MNT & H&B
  - Phase 2 Every 2 weeks X 6
  - Minimum 1 MNT & H&B follow up
  - Phase 3 Monthly X 6
  - Minimum 1 MNT & H&B follow up
  - Phase 4 Ongoing
  - (usually every 2-6 weeks)
- Focused curriculum
- Each visit building on previous visit
- Family focused

Clinical Considerations Regarding the Use of Obesity Pharmacotherapy in Adolescents with Obesity.

Obesity (Silver Spring). 2019 Feb;27(2):190‐204.
Baseline Evaluations

- Key History: +FHx of obesity, HTN, T2DM, Sleep-nocturnal enuresis, medications – wt promoting, co-occurring dxs,
- Lab Screening: lipids, LFTs, FBG, HgbA1c
  (at least by age 10yrs for pts with OW/obesity, younger if severe obesity & FHx of hyperlipidemia, T2DM, etc)
- Request adding updated BMI curve to include % of the 95th% to EMR

Current and Emerging Treatments of Obesity

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>Pharmacological</th>
<th>Medical Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low calorie diet</td>
<td>Vagus nerve block</td>
<td>Adjustable gastric band</td>
</tr>
<tr>
<td>Low-carbohydrate diet</td>
<td>Gastric balloon</td>
<td>Dopetraline</td>
</tr>
<tr>
<td>Low glycemic index diet</td>
<td>Gastric aspiration</td>
<td>Endoscopic</td>
</tr>
<tr>
<td>Pales diet</td>
<td>Endoscopic</td>
<td>Thoracic endoscopy</td>
</tr>
<tr>
<td>Mediterranean diet</td>
<td>Gastric stenting</td>
<td>Multisite bariatric surgery</td>
</tr>
<tr>
<td>Very low calorie diet</td>
<td>Gastric creation</td>
<td>Sleeve gastrojejunostomy</td>
</tr>
<tr>
<td>Aerobic exercise</td>
<td>Gastric bypass</td>
<td>Gastric bypass</td>
</tr>
<tr>
<td>Resistance training</td>
<td>Sleeve gastrectomy</td>
<td>Sleeve gastrectomy</td>
</tr>
<tr>
<td>Sleep enhancement</td>
<td>Gastric bypass</td>
<td>Sleeve gastrectomy</td>
</tr>
<tr>
<td>Circadian enhancement</td>
<td>Sleeve gastrectomy</td>
<td>Sleeve gastrectomy</td>
</tr>
<tr>
<td>Motivational interviewing</td>
<td>Sleeve gastrectomy</td>
<td>Sleeve gastrectomy</td>
</tr>
<tr>
<td>Stress reduction</td>
<td>Sleeve gastrectomy</td>
<td>Sleeve gastrectomy</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy</td>
<td>-</td>
<td></td>
</tr>
</tbody>
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FDA- Approved Anti-Obesity Pharmacotherapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>MOA</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Naltrexone agon</td>
<td>16yrs and older</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Lipase inhibitor</td>
<td>12 yrs and older</td>
</tr>
<tr>
<td>Liraglutide (Saxenda)</td>
<td>GLP-1 agonist</td>
<td>12 yrs and older</td>
</tr>
<tr>
<td>Semaxanotide</td>
<td>MC4R agonist</td>
<td>6 yrs and older</td>
</tr>
<tr>
<td>*Semaglutide (Wegovy)</td>
<td>GLP-1 agonist</td>
<td>Trials underway</td>
</tr>
</tbody>
</table>

Anti-Obesity Medications and Pediatrics

- Medications FDA-approved for indications of obesity in children exist
  • many Medicaid & private insurers do not cover currently
- Medications FDA-approved for indications of obesity in children:
  • Phentermine 16 years and older
  • Orlistat 12 years and older
  • Liraglutide 12 years and older at 1.8mg dose
  • Setmelanotide 6 years and older
- Alternatives:
  • Phentermine (S) + topiramate (S) = Qsymia (SSS)
  • Wellbutrin (S) + naltrexone (S) = Contrave (SSS)
  • off label or if patient on Wellbutrin for depression
- For Binge Eating Disorder/Loss of Control eating + ADHD
  • 1st line Lisdexamfetamine
- For Pre-Diabetes, Type 2 diabetes, Insulin resistance
  • GLP-1 at 1.8mg dose

Weight Loss Varies Widely Among Patients

<table>
<thead>
<tr>
<th>Diet (Low-carbohydrate)</th>
<th>Drug (Liraglutide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>Patients (%)</td>
</tr>
<tr>
<td>Diet (%)</td>
<td>Drug (%)</td>
</tr>
</tbody>
</table>

37 38 39 40 41 42
When Obesity is treated: Anti-Obesity Tools

Metabolic & Bariatric Surgery

Review Barriers to Obesity Treatment
- Obesity as a physiologically-driven disease
- Education for Providers, Policy makers, Leadership, Patients
- Ongoing robust research is promising
- Increasing amount and variety of tools
- Need financial coverage

Major challenges to effective obesity care

Starting a healthy conversation about obesity
Hopeful Thoughts

WOW Thanks You!

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The Co-occurrence of Pediatric Obesity and ADHD: an Understanding of Shared Pathophysiology and Implications for Collaborative Management

Abstract
To describe what is known about the association between obesity and attention deficit hyperactivity disorder (ADHD) in children along with the co-occurring conditions of sleep disturbance, loss of control/intuitive eating disorder (LOC-IED) and anemia.

Teledicine as a tool

The pediatric weight management office visit via teledicine: pre-to post-COVID-19 pandemic
**Prevalence**

- Overweight & obesity affected 32% of the U. S. youth aged 2 to 19 years in 2012 (NHANES). 2
  - Preschool children (2-5 years old)
    - 14.5% overweight
    - 14.6% obesity
  - School aged children (6-11 years)
    - 14.6% overweight
    - 14.6% obesity
  - Adolescents 12 to 19 years of age
    - 18.9% overweight
    - 13.7% obesity

- Prevalence by Obesity Class (2014 NHANES): 1
  - 17.4% of children met criteria for class I obesity (11.7 million children)
  - 4.3% for class II (Severe obesity)
  - 2.4% for class III (Severe obesity)

A clear, statistically significant increase in all classes of obesity continued from 1999 through 2014. 2

- Severe obesity (Class II & III) is the fastest-growing subcategory of obesity in youth.

Ogden, Carroll, Kit, et al. (2014) 1; Skinner, Perrin, Siekkinon (2016) 1; Kelly et al. (2013) 1; Ogden, Carroll, Fryar, et al. (2015) 1

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**WOW Presentations**

1. OMA Telemedicine Webinar: Oct 2018
2. POWER Presentations on Telemedicine for Pediatric Obesity: Feb 2019
4. Obesity Pathophysiology: Let's Go ONLINE Seminar: Jan 2019
5. Obesity Pathophysiology for AMEO Adult students: April 2019 and ongoing
7. AAP Obesity Course: April 2019 Pathophysiology & Case Presentations
8. OMA Webinar: The Co-Occurrence of Pediatric Obesity & ADHD 2020
9. NR: AAP Conference: The Co-Occurrence of Pediatric Obesity & ADHD
10. TOS/Obesity Week Lessons Learned: Pediatric Obesity Telemedicine: Jan 2021
11. Practical Implementation of Pediatric Obesity Care: SBO Advanced Therapies for Pediatric Obesity: Feb 2020