Metabolic Syndrome Across the Life Cycle-After Reproduction Age

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Disclosure:

- No financial disclosure.
- No off brand medication use.
Objectives

- Brief review Physiology of peri-menopausal and menopausal transition period.
- Discuss physiology of obesity and functionality of adipose cell.
- Discuss Obesity and how it relates to Metabolic Syndrome.
- Outline Treatment overview of Obesity and Metabolic Syndrome.
### Menarche to FMP (0)

<table>
<thead>
<tr>
<th>Stage</th>
<th>REPRODUCTIVE</th>
<th>MENOPAUSAL TRANSITION</th>
<th>POSTMENOPAUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>-4</td>
<td>-3b</td>
<td>-3a</td>
</tr>
<tr>
<td>Terminology</td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
</tr>
<tr>
<td>Duration</td>
<td>variable</td>
<td>variable</td>
<td>1-3 years</td>
</tr>
</tbody>
</table>

#### Principal Criteria

- **Menstrual Cycle**: Variable to regular, regular, regular, variable
- **Subtle changes in Flow/Length**: Persistent ≥7-day difference in length of consecutive cycles
- **Interval of amenorrhea of >=60 days**

#### Supportive Criteria

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>FSH</th>
<th>AMH</th>
<th>Inhibin B</th>
<th>Antral Follicle Count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;25 IU/L</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Stabilizes</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Low</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

#### Descriptive Characteristics

- **Symptoms**: Blood draw on cycle days 2-5
- **Elevated**: Vasomotor symptoms
- **Likely**: Increasing symptoms of urogenital atrophy

**FIG. 2.** The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.

Key hormonal changes in Menopausal Transition (MT)

- During MT, follicles become more resistant to gonadotropins stimulation → FSH and LH levels will increase → leading to stromal stimulation of the ovary → increase in estrone levels and decrease in estradiol levels.

- Granulosa cells producing inhibin in the ovary will decease in production as a result of negative feedback of elevated FSH levels.

- The most significant decrease is noted in the levels of estradiol, spanning from 2 years before final menstrual period (FMP) till 4 years after FMP.

- Total serum testosterone does not change with MT

- DHEAS decline with age

- No specific changes in thyroid function related to menopause have been found.

- A trend in rising total cholesterol, LDL and apolipoprotein B levels in conjunction of loss of protective effect of HDL is noted.

Physiologic Changes and Symptoms during MT:

- Hot flashes of flushes (Most common)
- Insomnia
- Weight gain and bloating
- Mood changes
- Irregular menses
- Mastodynia
- Depression
- Headache

Menopause and Development of Comorbidities

Menopause is associated with increased risk and development of:

- Cardiovascular problems/Coronary artery disease
- Breast cancer
- Osteoporosis
- Gynecological cancers
- Central nervous system diseases
- Obesity and metabolic syndrome

The National Health and Nutrition Examination Survey (NHANES) data found that:

- 51.7 percent of women ages 20-39 were classified as “overweight” or “affected by obesity”
- 68.1 percent of women ages 40-59 were classified as “overweight” or “affected by obesity”

During the time of perimenopausal and MT time occurs, women start losing muscle mass but fat storage tends to increase; thus, body composition tends to put women at higher risk for development of metabolic disease (especially heart disease and diabetes).
Leading cause of death in postmenopausal women.

The beneficial effect of estrogen on CAD and mortality is due to many factors but one prominent mechanism noted was the effect of estrogen on lipid metabolism. Estrogen decreases LDL and increases HDL \( \rightarrow \) some studies noted that the best predictors of CAD in men and women are different and triglycerides, HDL and Lipoprotein(a) may be more significant in women.

SWAN is a multiethnic, community based, longitudinal cohort study of natural history of menopause transition of 3302 women at 7 sites in the US.

Noted finding was development of metabolic syndrome, with its multiple co-morbid risks, was probably as a result of progressive androgenicity of the hormonal milieu. Which is different than current thought of a result in decline of estrogen.

Testosterone predominance was significantly and independently linked to 3 out 5 components of metabolic syndrome: elevated WC, triglyceride, and decrease HDL.

Adjusted odds of changes in hormones or hormone measure for prediction of incident of metabolic syndrome

<table>
<thead>
<tr>
<th>Hormone or hormone surrogate</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>0.98 (0.88-1.08)</td>
<td>0.40</td>
</tr>
<tr>
<td>Bioavailable testosterone</td>
<td>1.10 (1.01-1.20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex-hormone-binding globulin</td>
<td>0.87 (0.81-0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.97 (0.88-1.06)</td>
<td>0.49</td>
</tr>
</tbody>
</table>
New onset Metabolic syndrome was noted by the time of Final Menstrual Period (FMP) in 13.7% of the cohort. But it not associated with levels of either total testosterone or total estradiol.

New onset Metabolic syndrome was found significantly associated with changes in bioavailable testosterone. “For every 1SD increase in bioavailable testosterone levels, the odds of developing metabolic syndrome increased by 10%.”
Obesity Epidemic Prevalence Map

Higher prevalence found in the South (30.2%) and Midwest (30.1%)

Lower prevalence noted in the Northeast (25.6%) and West (24.9%)

Source: Behavioral Risk Factor Surveillance System, CDC.
https://www.cdc.gov/obesity/data/prevalence-maps.html
Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2015

Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.
Adipose Cells and Physiology

Normal Adipocytes

Over nutrition
Metabolic syndrome
Genetics

↓ Adipocytes

Effects

Autocrine
- Insulin sensitivity
- Glucose/lipid transport
- Adipokine secretion
- IL-6
- Adiponectin
- TNFa

Paracrine
- Immune cell attraction
- Differentiation
- Cell growth
- Insulin sensitivity
- Adipokine secretion
- MCP-1, progranulin
- Dkk-1
- Chemerin
- Adiponectin
- TNFa

Endocrine/Systemic
- Regulation of appetite/satiety
- Systemic insulin sensitivity
- Insulin secretion
- Endothelial function
- Inflammation
- Liver fat
- Cardiomyocyte contraction
- Fat deposition
- Leptin
- Adiponectin
- Leptin
- Omentin
- Resistin, chemerin
- Fetuin-A
- FABP4
- RBP4

Adipokines
- Leptin
- Adiponectin
- Visfatin/Nampt/PBEF
- Vaspin
- RBP4
- FGF21
- BMP4
- Resistin-1
- Cathespin
- Apelin
- Omentin
- Lipocalin
- and hundreds more

Proteins of RAS
- Angiotensinogen

Endocannabinoids and other lipids
- Arachidonic acid
- 2-AG
- Free fatty acids

Leandro C.; Front Physiology. Adipokins, diabetes and atherosclerosis: an inflammatory association. 03 Nov 2015
Obesity leading to Insulin Resistance

Leandro C.; Front Physiology, Adipokins, diabetes and atherosclerosis: an inflammatory association. 03 Nov 2015
Pleiotropic nature of Leptin

## Is Obesity a Disease?

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Obesity is a complex, <strong>multifactorial disease</strong> that develops from the interaction between genotype and the environment. Our understanding of how and why obesity occurs is incomplete; however, it involves the <strong>integration of social, behavioral, cultural, and physiological, metabolic, and genetic factors</strong>”</td>
<td>“...If obesity is truly a disease, then over 78 million adults and 12 million children in America just got classified as sick...Everyone has friends and acquaintances who now qualify as diseased. Yet many sensible people, from physicians to philosophers, know that declaring obesity a disease is a mistake. Simply put, obesity is not a disease. To be sure, it is a <strong>risk factor for some diseases</strong>. But it would be false to say that everyone who is obese is sick as to say that every normal weight person is well”</td>
</tr>
</tbody>
</table>

1998 - National Heart, Lung, and Blood Institute (NHLBI)

2013 - American Academy of Family Physicians

2013 - Richard B. Gunderman, MD, PhD
The Disease of Obesity

American Medical Association position statement in 2014:
“Recognizing obesity as a disease will help change the way the medical community tackles this complex issue that affects approximately one in three Americans”
Obesity Related Disorders

Medical Complications of Obesity

- Pulmonary disease
  - abnormal function
  - obstructive sleep apnea
  - hypoventilation syndrome

- Idiopathic intracranial hypertension
  - Stroke
  - Cataracts

- Nonalcoholic fatty liver disease
  - steatosis
  - steatohepatitis
  - cirrhosis

- Gall bladder disease

- Gynecologic abnormalities
  - abnormal menses
  - infertility
  - polycystic ovarian syndrome

- Osteoarthritis

- Skin

- Gout

- Severe pancreatitis

- Cancer
  - breast, uterus, cervix
  - colon, esophagus, pancreas
  - kidney, prostate

- Diabetes

- Dyslipidemia

- Hypertension
During MT, increase in fat depositions especially in the intrabdominal area (aka Visceral fat) is noted with little change to muscle mass.

It is thought that visceral fat cells have direct access to portal blood entering the liver and carry a significant source of many of proinflammatory proteins and are responsible for increase cardiovascular heart disease. This increase was suppressed in pre-menopausal state due to anti-inflammatory protection of estrogen.

Visceral obesity correlates closely to an increase in insulin resistance → elevated insulin → abnormal glucose metabolism → reduction in fat breakdown and stimulation of more fat storage/deposition.
Visceral adipose and inflammation: Adipose tissue is an ACTIVE ENDOCRINE ORGAN secreting adipokines, producing increased low level systemic inflammation that promote metabolic-associated pathologies such as atherosclerosis.
Influence of Fat distribution on Cardiometabolic Risk

Subcutaneous obesity
“Healthy” adipose tissue

Visceral obesity
Dysfunctional adipose tissue

Normal metabolic profile
Absence of metabolic Syndrome clinical criteria

Altered metabolic profile
Presence of metabolic Syndrome clinical criteria (Hypertiglyceridemia and increase waist)

Jean-Pierre Despres Circulation. 2012; 126:1301-1313
Obesity and Insulin Resistance relevance to Heart Disease and Heart Failure

- Obesity has been associated with alternations in the Myocardium structure and Arterial wall remodeling, which leads to LV dysfunction (from Increased cardiac output) and Increased risk of Heart Failure
- Increased intra-myocardial Fatty acid deposition
- For each incremental increase of BMI by 1 unit, there is an increase risk of HF developing by 5% in men and 7% in women

Obesity, Inflammation and postmenopausal breast cancer

Obesity-associated factors, including leptin, insulin and inflammatory mediators, seem to influence breast cancer growth and prognosis independently of estrogens and at least in part by interacting with estrogen signaling at a cellular level.

Metabolic Syndrome

National Heart, Lung, Blood Institute (NHLBI) and American Heart Association (AHA) define metabolic syndrome when three of the following five are met:

1. waist circumference greater than 88 cm
2. HDL-C less than 50 mg/dL
3. Triglyceride greater than 150 mg/dL
4. Blood pressure above 130/85 mmHg
5. Fasting blood glucose over 110 mg/dL

While the greatest risk of metabolic syndrome is cardiovascular disease this risk was also noted to be age related.

- 22% of general population meet criteria
- 60% of postmenopausal women are affected

Mathew J, J Am Heart Assoc. 2016;5:e003609 NHLBI American Heart Association
Determinants of Body Weight

- **Genes**
  - Protective and at risk alleles for weight gain
  - Race (ancestral admixture)
  - Gene-gene interactions

- **Biological factors**
  - In utero environment
  - Birth weight
  - Gender
  - Age
  - Concurrent diseases

- **Environment**
  - Food availability
  - Food quality
  - Built environment
  - Socioeconomic status
  - Education

- **Behavior**
  - Dietary preferences
  - Physical activity
  - Psychological factors
  - Cultural factors
  - Diurnal life patterns
Increase Energy Intake – Ingestion of: Proteins, Fats, Carbohydrate

Cause of Obesity: Abnormal Energy Balance

Decrease Energy Expenditure – Decrease in metabolic rate – Decrease in physical activity – Decrease energy to metabolize food

Body Weight

 Regulation of Food Intake

Central Signals
- Stimulate: NPY, AgRP, Orexin-A, MCH, Cannabinoids
- Inhibit: POMC, CART, α-MSH, CRH, Oxytocin, GLP-1, NE/CCK

Peripheral signals
- Glucose/AA/FA
- CCK, GLP-1, PYY, Oxyntomodulin
- Vagal afferents
- Insulin, Glucagon, PP, Amylin
- Leptin
- Ghrelin
- Cortisol
- Gut bacteria

Peripheral Organs
- GI Tract
- Adipose
- Adrenals
- Eye, nose, tongue, ears?

Brain

Modulating Factors
- Liking (palatability)
- Wanting (reward, addiction)
- Emotions
- Cues, habits, stress, portion
- Environment/Lifestyle
- Circadian rhythms
- Executive Function (frontal cortex)

Food intake
Complexities of Appetite Regulation

APRQ: agouti-related peptide; α-MSH: α-melanocyte-stimulating hormone; GHSR: growth hormone secretagogue receptor; INSR: insulin receptor; LeprR: leptin receptor; MC4R: melanocortin-4 receptor; NPY: neuropeptide Y; POMC: proopiomelanocortin; PYY: peptide YY; Y1R: neuropeptide Y1 receptor; Y2R: neuropeptide Y2 receptor. Apovian CM, Aronne LJ, Bessesen D et al. / Clin Endocrinol Metab. 2015;100:342-362.
Complex Biology of Obesity

Obesity related pathway signaling
Obesity is a result of a battle of forces

Life Style Modifications

- Healthy Diet
- Regular physical activity
- Improved and more sleep
- Stress reduction
- Stable eating patterns
- Weight stabilizing alternatives

Body fat mass set point

- Abnormal dietary constituents
- Unhealthy muscles
- Sleep deprivation
- Stress
- Disrupted circadian rhythms
- Weight gain inducing medications
1. Achieve an effective treatment to reduce the elevated fat mass set point
2. Recognizing and addressing the wide heterogeneity in the causes and manifestations of obesity
3. This result in a wide patient to patient variability in the response to all anti-obesity therapies
4. Patients who respond to one therapy might not show the same response to another.
5. Best is to match each patient with the most effective treatment to them
Evaluation of Patient affected by Obesity Disease

**History:**
- Medical
- Psychological
- Surgical, Gynecological
- Family
- Social
- Nutrition
- Physical Activity
- Review of Systems
- Medications/Supplements

**Physical Exam:**
- Age, race, gender, ethnicity
- Physical Exam
- Body Composition
- Laboratory
- Radiology
- Cardiology, Pulmonary, Sleep, other
- Diagnostic Staging

**Gender Related History:**

**Females:**
- Menstrual, menopause
- Fertility issues
- Pregnancy issues
- Contraception
- Cancer screenings
- Hormonal medications
- Hirsuitism, acne, etc.

**Males:**
- Andropause
- Gynecomastia
- Fat distribution
- Erectile dysfunction

**Both:**
- Sexual quality of life
- Birth history and early childhood feeding Hx
- Hygiene Issues
Example of common medications promoting weight gain:

1. CNS Drugs:
   a. Atypical Antipsychotics: Olanzapine
   b. Anti-epileptics: Valproate
   c. Mood stabilizer: Lithium
   d. Anti-depressants: SSRI (paroxetine), Tricyclic agents (Nortriptyline)
   e. Miscellaneous: Venlafaxine and mirtazapine

2. Endocrine agents:
   a. Glucocorticoids: prednisone
   b. OCP: medroxyprogesterone
   c. Diabetic agents: Insulin, Sulfonylureas (glyburide), Thiazolidinediones (pioglitazone)

3. Miscellaneous:
   a. Beta blockers: metoprolol
   b. Antihistamines: diphenhydramine
   c. Sleep aids: zolpidem
Effect of sleep on obesity regulation

- Timings
- Duration
- Nocturnal awakenings
- Quality
- OSA Screen
- Sleep Hygiene Tips

Sleep Hygiene Instructions

1. Avoid caffeine, nicotine, alcohol
2. Make bedroom sleep-inducing
3. Establish soothing pre-sleep routine
4. Go to bed when truly tired
5. Don’t be a night-time clock-watcher
6. Use light to your advantage
7. Be consistent with sleep schedule
8. Nap early or not at all
9. Lighten up on evening meals
10. Balance fluid intake
11. Exercise early
12. Follow thru

http://healthysleep.med.harvard.edu/healthy/getting/overcoming/tips

Knutson et al. Sleep Med Rev. 11(3): 163-78. 2007
Assess for the presence of obesity, adiposopathy, fat mass disease

Obesity may be assessed using several criteria (thresholds vary based on gender and ethnic differences):

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Male Threshold</th>
<th>Female Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body Mass Index (BMI)</strong></td>
<td>18.5-24.9 kg/m²</td>
<td>25.0-29.9 kg/m²</td>
</tr>
<tr>
<td><strong>Percent Body Fat</strong></td>
<td>Male: &lt;25%</td>
<td>Female: &lt;32%</td>
</tr>
<tr>
<td></td>
<td>Male: &gt;25%</td>
<td>Female: &gt;32%</td>
</tr>
<tr>
<td><strong>Waist Circumference</strong></td>
<td>Male: &lt;40 in.</td>
<td>Female: &lt;35 in.</td>
</tr>
<tr>
<td></td>
<td>Male: &gt;40 in.</td>
<td>Female: &gt;35 in.</td>
</tr>
<tr>
<td><strong>Edmonton Obesity Staging System</strong></td>
<td>Stage 0, 1, 2, 3, 4</td>
<td></td>
</tr>
</tbody>
</table>

## Prevention
- **No Obesity**
- **Overweight**
  - Primary care provider or dietitian
  - If treatment is ineffective, refer to an obesity medicine specialist.
- **Obesity**
  - Class I: BMI 30.0-34.9
  - Class II: BMI 35-39.9
  - Class III: BMI > 40.0
  - Consider referring to an obesity medicine specialist.
### Overview Treatment of Obesity

#### A Guide to Selecting Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>25–26.9</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>27–29.9</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>30–34.9</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>35–39.9</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>≥40</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>+</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>+</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>+</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>+</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>+</td>
</tr>
<tr>
<td>Appropriate NHLBI Guidelines</td>
<td>+</td>
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<td>Appropriate NHLBI Guidelines</td>
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<td>Appropriate NHLBI Guidelines</td>
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<td>+</td>
</tr>
<tr>
<td>Appropriate NHLBI Guidelines</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>No</td>
</tr>
<tr>
<td>With comorbidities</td>
<td>+</td>
</tr>
<tr>
<td>With comorbidities</td>
<td>+</td>
</tr>
<tr>
<td>With comorbidities</td>
<td>+</td>
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<tr>
<td>With comorbidities</td>
<td>+</td>
</tr>
<tr>
<td>Surgery</td>
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<td>No</td>
<td>No</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>No</td>
<td>With comorbidities</td>
</tr>
<tr>
<td>Surgery</td>
<td>No</td>
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<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>No</td>
<td>With comorbidities</td>
</tr>
<tr>
<td>Surgery</td>
<td>No</td>
</tr>
</tbody>
</table>

#### Chart:

- **Lifestyle Modifications**
- **Medications**
- **Bariatric Surgery**

## Recommendation for Therapeutic Weight Loss

<table>
<thead>
<tr>
<th>OBESITY COMPLICATION</th>
<th>% weight loss required for therapeutic benefit</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention</td>
<td>3% to 10%</td>
<td>Maximum benefit 10%</td>
<td>DPP (Lancet, 2009)  SEQUEL (Garvey et al, 2013)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5% to &gt;15%</td>
<td>BP still decreasing &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3% to &gt;15%</td>
<td>TG still decreasing at &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>3% to &gt;15%</td>
<td>HbA1c still decreasing at &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>10%</td>
<td>Improves steatosis, inflammation, mild fibrosis</td>
<td>Assy et al, 2007; Dixon et al, 2004; Anish et al, 2009</td>
</tr>
<tr>
<td>Sleep Apnea (AHI)</td>
<td>10%</td>
<td>Little benefit at ≤ 5%</td>
<td>Sleep AHEAD (Foster, 2009)  Winslow et al, 2012</td>
</tr>
<tr>
<td>Stress Incontinence</td>
<td>5-10%</td>
<td></td>
<td>Burgio et al, 2007  Leslie et al, 2009</td>
</tr>
<tr>
<td>GERD</td>
<td>5-10% women 10% men</td>
<td></td>
<td>Singh et al, 2013  Tutuljan R, 2011</td>
</tr>
</tbody>
</table>
But first: patient readiness to change

Is the patient ready and motivated to lose weight? Evaluation of readiness should include the following:

1) reasons and motivation for weight loss
2) previous attempts at weight loss
3) support expected from family and friends
4) understanding of risks and benefits
5) attitudes toward physical activity
6) time availability
7) potential barriers to the patient’s adoption of change
5 A's of Obesity Management

| Ask | - Ask for permission to discuss body weight  
|     | - Explore readiness for change |
| Assess | - Assess BMI, WC, and Obesity stage  
|     | - Explore drivers and complications of excess weight |
| Advice | - Advice the patient about the health risks of obesity, the benefits of modest weight loss, the need for long-term strategy, and treatment options |
| Agree | - Agree on realistic weight-loss expectations, targets, behavioral changes, and specific details of the treatment plan. |
| Arrange/Assist | - Assist in identifying and addressing barriers; provide resources, assist in finding and consulting with appropriate providers; arrange regular follow up. |

Goals of therapy are to reduce body weight and maintain a lower body weight for the long term; the prevention of further weight gain is the minimum goal.

1) An initial weight loss of 5-10 percent of body weight achieved over 6 months is a recommended target.

2) The rate of weight loss should be 1 to 2 pounds per week.

3) Greater rates of weight loss do not achieve better long-term results.

4) After the first 6 months of weight loss therapy, the priority should be weight maintenance achieved through combined changes in diet, physical activity, and behavior.

5) Further weight loss can be considered after a period of weight maintenance.
Key Components of Lifestyle Therapy

- Dietary Therapy
- Physical Therapy
- Cognitive behavioral therapy

New Treatment Paradigm is by treating WEIGHT FIRST then Comorbidities
Pharmacological Therapy

- Review current medications and identify ones that can cause an increase in weight.
- Discuss with primary care and specialists to consider and change medications to alternate medications that are weight neutral or weight reducing medications.
- Initiate weight loss medication after establishing lifestyle modification goals and plans.
- Reevaluate medication every 3 month to assure benefits. Stop medication if appropriate weight loss was not achieved or side effects arise.
Pharmacotherapun

Examples of anti-obesity medications approved in 1999 or before

- Phentermine
- Diethylpropion
- Phendimetrazine
- Benzphetamine
- Orlistat

Examples of anti-obesity medications approved in 2012 and beyond

- Lorcaserin
- Phentermine HCL/topiramate extended release
- Naltrexone HCL/bupropion HCL extended release
- Liraglutide
FDA approved meds for Obesity in the US as of 2016

<table>
<thead>
<tr>
<th>Medication</th>
<th>Average Weight Loss*</th>
<th>Mechanism of Action</th>
<th>Potential Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine (Adipex™, Ionamin™)</td>
<td>~ 5%</td>
<td>Adrenergic</td>
<td>Tachycardia, hypertension</td>
</tr>
<tr>
<td>Phentermine / Topiramate (Qsymia™)</td>
<td>10%</td>
<td>Adrenergic, CNS</td>
<td>Tachycardia, hypertension, cognitive dysfunction, neuropathy, teratogenicity</td>
</tr>
<tr>
<td>Bupropion / Naltrexone (Contrave™)</td>
<td>4.5%</td>
<td>CNS: opioid antagonism</td>
<td>Seizures, confusion, anxiety, opiate withdrawal</td>
</tr>
<tr>
<td>Lorcaserin (Belviq™)</td>
<td>3.5%</td>
<td>Serotonergic (5HT₂C)</td>
<td>Headache</td>
</tr>
<tr>
<td>Liraglutide (Saxenda™)</td>
<td>7%</td>
<td>GLP-1 agonist</td>
<td>Nausea</td>
</tr>
<tr>
<td>Orlistat (Xenical™)</td>
<td>3%</td>
<td>Lipase inhibitor</td>
<td>Steatorrhea, incontinence</td>
</tr>
</tbody>
</table>
New Treatment Paradigm: WEIGHT FIRST

<table>
<thead>
<tr>
<th>Overweight/Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitor</strong></td>
</tr>
<tr>
<td><strong>Diet</strong></td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
</tr>
<tr>
<td><strong>Mods</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dys-lipidemia</th>
<th>HTN</th>
<th>IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitor</strong></td>
<td>Lipid panels</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td>Lipoproteins subsets</td>
<td>Ambulatory</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td>↓ Sat + trans fat</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td>↑ Omega-3s</td>
<td>DASH Diet</td>
</tr>
<tr>
<td></td>
<td>↑ MUFA</td>
<td>↓ Sodium</td>
</tr>
<tr>
<td></td>
<td>↓ Simple CHO</td>
<td>↓ ETOH</td>
</tr>
<tr>
<td></td>
<td>↓ ETOH</td>
<td></td>
</tr>
<tr>
<td><strong>Mods</strong></td>
<td>Statins</td>
<td>ACE Inhibitors</td>
</tr>
<tr>
<td></td>
<td>Fibrates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Drug-Associated Weight Change Reference

<table>
<thead>
<tr>
<th>Therapeutic Category</th>
<th>Drug Class</th>
<th>May Cause Weight Gain</th>
<th>Alternatives That Cause Less Weight Gain, Weight Loss, or are Weight Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatry</strong></td>
<td>Antipsychotic</td>
<td>• Clozapine *• Risperidone • Olanzapine • Quetiapine • Other</td>
<td>• Ziprasidone • Aripiprazole</td>
</tr>
<tr>
<td></td>
<td>Antidepressants and Mood Stabilizers</td>
<td>• Citalopram • Escitalopram • Fluoxetine • Lithium • MAOIs</td>
<td>• Bupropion • Neftazodone • Fluoxetine (short term: &lt;1 year) • Sertraline (short term: &lt;1 year)</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td>Anticonvulsants</td>
<td>• Carbamazepine • Gabapentin • Valproate</td>
<td>• Lamotrigine • Topiramate • Zonisamide</td>
</tr>
<tr>
<td><strong>Endocrinology</strong></td>
<td>Diabetes Treatments</td>
<td>• Insulin • Sulfonylurea • Thiazolidinedione</td>
<td>• Metformin • Acarbose • Miglitol • Pramlintide • Exenatide • Sitagliptin</td>
</tr>
<tr>
<td><strong>Obstetrics &amp; Gynecology</strong></td>
<td>Oral Contraceptives</td>
<td>• Progestational steroids • Hormonal contraceptives containing progestational steroids</td>
<td>• Barrier methods • IUDs</td>
</tr>
<tr>
<td></td>
<td>Endometriosis Treatment</td>
<td>• Depot leuprolide acetate</td>
<td>• Surgical methods</td>
</tr>
<tr>
<td><strong>Cardiology</strong></td>
<td>Antihypertensives</td>
<td>• β-blocker • ACE inhibitors • Calcium channel blockers</td>
<td>• Lisinopril • Captopril • Hydralazine</td>
</tr>
<tr>
<td><strong>Infectious Disease</strong></td>
<td>Antiretroviral Therapy</td>
<td>• Protease inhibitors • AZT • NVP • boosted ritonavir • other boosted ARTs</td>
<td>• None</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td>Steroid Hormones</td>
<td>• Corticosteroids • Progestational steroids • Norethisterone</td>
<td>• NSAIDs</td>
</tr>
<tr>
<td></td>
<td>Antihistamines/ Anticholinergics</td>
<td>• Diphenhydramine • Doxepin • Cyproheptadine • Other potent antihistamines</td>
<td>• Decongestants • Irritant inhalers</td>
</tr>
</tbody>
</table>
# Bariatric Surgical Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pros</th>
<th>Cons</th>
<th>Expected loss in percent excess body weight* at two years</th>
<th>Optimally suited for patients with:</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roux-en-Y Gastric Bypass</td>
<td>Greater improvement in metabolic disease</td>
<td>Increased risk of malabsorptive complications over sleeve</td>
<td>60-75%</td>
<td>Higher BMI, GERD, Type 2 DM</td>
<td>Largest data set, more technically challenging than LAGB, VSG</td>
</tr>
<tr>
<td>Vertical Sleeve Gastrectomy</td>
<td>Improves metabolic disease; maintains small intestinal anatomy; micronutrient deficiencies infrequent</td>
<td>No long term data</td>
<td>50-70% (*3-year data)</td>
<td>Metabolic disease</td>
<td>Can be used as the first step of staged approach; most common based on 2014 data</td>
</tr>
<tr>
<td>Laparoscopic Adjustable Gastric Banding</td>
<td>Least invasive; removable</td>
<td>25-40% 5 year removal rate internationally</td>
<td>30-50%</td>
<td>Lower BMI; no metabolic disease</td>
<td>Any metabolic benefits achieved are dependent on weight loss</td>
</tr>
<tr>
<td>Biliopancreatic Diversion with Duodenal Switch</td>
<td>Greatest amount of weight loss and resolution of metabolic disease</td>
<td>Increased risk macro- and micronutrient deficiencies over bypass</td>
<td>70-80%</td>
<td>Higher BMI, Type 2 DM</td>
<td>Most technically challenging</td>
</tr>
</tbody>
</table>

*Excess body weight (EBW) = (total body weight) - (lean body weight)
Metabolic Syndrome and Obesity Tree

Obesity and Metabolic disease treatment is an energy balance that is much more about the physiology (signaling and homeostasis) than the physics (calories in and out).

The driving forces to consume food (whether it is homeostatic, hedonic or both) and the autonomic thermogenesis are more a response to the body’s perceived needs than primary driver of fat mass and weight.
Obesity is a disease that could present at any point in a patient’s life and it is a chronic disease.

Peri and Post menopausal women tend to have higher incidence of obesity and metabolic syndrome related health problems.

Hormonal treatment for women is a good initial step in treatment of the symptoms of menopause but not enough to address obesity. Practitioners should address risk factors that lead to obesity and educate patients about prevention and treatment of obesity and metabolic syndrome prior to menopause.

Refer to obesity medicine specialist or bariatric surgeon for additional help.
Thank you