Obesity Pathophysiology and Treatment

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Introduction

Calories in, Calories out, right?

- Although it may seem simple, the pathophysiology of obesity is complex, with many layers. This lecture is abbreviated, and meant to be an introduction to this fascinating topic.

- Today's goal is not only to understand obesity and its pathophysiology better, but to understand your patients that have obesity better.

Disclosures

- I am a person of size. Therefore, I have some bias, having had direct experiences related to this presentation.
- There are no financial disclosures.

Implicit Bias

In order to meet the requirements for the State of Michigan regarding implicit bias training, a pretest and posttest must be administered, and verified by the organization, before issuing implicit bias CME credit. A link will pop up early on in this lecture, then later at the end for these assessments. Following Completion of the posttest, you should receive feedback regarding answers.

The Case of Stomach Ulcers.

In the past many believed that stomach ulcers were caused by stress. There was some evidence for this, like the Gray, et. al. (1951) article, that established a reasonable explanation for this. And this belief was ubiquitous.

- An entire body of knowledge of treatment was based on this until two Australian doctors, Barry Marshall and Robin Warren questioned this body of knowledge. Eventually they presented evidence on H. Pylori causing ulcers, and progress in treatment could be made, though reluctantly. (Weintraub, 2010)
- Marshall says about it:
 - "No, it sat there as a hypothesis for another 10 years. Some patients heard about it, but gastroenterologists still would not treat them with antibiotics. Instead, they would focus on the possible complications of antibiotics. By 1985 I could cure just about everybody, and patients were coming to me in secret—for instance, airline pilots who didn't want to let anyone know that they had an ulcer." (Weintraub 2010)
- Companies like Procter and Gamble (who made Pepto-bismol) derided his work and published questionable research. Eventually, it was established that H. Pylori is a common cause of ulcers, something we now take for granted.

Case of skin pigment

Skin pigment on humans is fascinating, loaded with social and cultural baggage, and has a continuum of physical representation.

- "Doctor, how can I lighten my skin?"
 - One might respond: "Stay out of the sun..."
 - Depending on their type (see image), how might this work?

(LeeJa, 2008)

	Fitzpatrick type I	Fitzpatrick type II	Fitzpatrick type III
	 Pale white skin. Always burns, never tans. 	 Fair white skin. Burns easily, minimal tan. 	 Darker white to olive skin. Sometimes burn, gradual tan.
,		6	0
,,	Fitzpatrick type IV	Fitzpatrick type V	Fitzpatrick type VI
"	Fitzpatrick type IV • Light brown skin. • Minimally burns, tans easily.	Fitzpatrick type V Oark brown skin. Rarely burns, darkly tans.	Fitzpatrick type VI Oark brown to black skin. Never burns, darkly tans.

How does all this connect to Obesity?

- Misconceptions and stigma regarding increased body weight have stymied research, just as they did for stomach ulcers, but this is changing.
- Besides inhibiting research, our own misconceptions and biases can inhibit patient care, just as they did with stomach ulcers.



 Like skin pigmentation, body weight is a complex physical phenomenon with a continuum of phenotype. We now know that this phenotype has many influences. This presentation will initiate an analysis of what is known as well as examining our biases.

Obesity Terminology

The word "Obesity", although used here as a specific medical term, has become laden with much stigma. As a result, though it may be used here for its specificity, it should probably be avoided with your patients.

Consider terms such as :

Person with increased body habitus

Person of size

Person with elevated BMI

Person with increased Adipose tissue

Person with increased body weight

And Others that focus on respect for the person as an individual

Pathophysiological Causes

There are several factors that contribute to the phenotype of increased body weight.

Genetic Factors in Obesity

- Starting in the late 1990's to the early 2000's, research on the genetic mechanisms of body weight started. People began asking the right questions to get more nuanced answers:

"With 300 million people now suffering from obesity worldwide, fat has become a global epidemic....The map they came up with looks like a flowchart from hell. Churchill's group identified a dozen sites in the mouse genome where genes are influencing the body weight of mice. But the genes have different effects. Some make mice large-bodied, and being big makes mice more likely to get fat. But they also found genes that had separate effects on both body size and fat levels. In some cases, the same gene could make a mouse both big and lean. Other genes influenced only how fat the mice were, with no effect on their body size. Still other genes determined the size of different fat pads. One region of mouse DNA appears to make mice fat overall while actually making the fat pads on their haunches smaller." (Zimmer 2007).

Genetic Factors in Obesity

- Prader-Willi Syndrome, is a frequently studied condition that has increased body weight as a component. It is well established that this syndrome is genetic (or epigenetic).
- This example offers confirmation that genes can affect body habitus, behavior and metabolism.
- (fwpr.org, retr.2022)



Genetic Factors in Obesity

One small corner of the mouse genome pathway that controls adipose tissue and body weight.

(Yazdi, et al, 2015)



<u>Genetic</u> Factors in Obesity

Genetic Loci are first identified as candidates for their role in any disease, primarily through Genome Wide Association Studies (GWAS). Once a candidate is found, it is possible to look deeper into its function using other techniques. The graph to the right, shows the number of potential candidates that we have now identified. (Nature.com, 2021)

 Each of these genes becomes a target for new medications to treat obesity(discussed more later)



Genetic Factors in Obesity

- Data supports the assertion that genetics plays a significant role in the continuum of body weight.
- Genetics alone would make this a very complex condition in itself, but it is only one of multiple etiological components of increased body weight.



Epigenetic Factors in Obesity

Epigenetics is defined by some sources as a phenotypic change as a result of modification of gene expression.

Every gene is influenced by epigenetics, including genes that regulate adipose tissue and body size and weight.

There are various endogenous mechanisms of epigenetic control in our gene system that allow our genes to function in a sensible manner. For example, Methylation and acetylation patterns, Histone Modification, and several others. However, <u>how</u> these are affected by the environment is a fascinating and relatively new area of study.

Epigenetic Factors in Obesity

Agouti mice can help us understand epigenetics.

- Agouti mice are bred to have a single gene mutation, the agouti related protein (AGRP), that affects melanocortin receptors. As a result, they are genetically obese, and have orange fur and are prone to diabetes.
- However, When agouti mice were fed food supplemented with extra methyl groups prior to and during conception, though their genes were agouti, their offspring were phenotypically normal. This classic Model demonstrates the role that epigenetics plays.
- (Wang, Majzoub, 2011)



Epigenetic Factors in Obesity

When does Epigenetic modification occur?

- It seems the epigenetic silencing in agouti mice occurred shortly before, and during conception.
- Our genes are most active (and therefore modifiable in terms of epigenetics), at conception, and then, there is a variable decline as we age.
- We can change some with epigenetics, but a difficult to quantify amount is minimally affected by current (later in life) environment, including at least some genes that regulate the continuum of body weight.
- One commonly discussed example is the possible association between smoking and diabetes and Obesity.
 - "Maternal smoking during pregnancy was associated in a dose-response manner with overweight and obesity in the daughter through adolescence and adult life. Smoking cessation during the first trimester appears to mitigate this excess risk." (Harris et. al, 2013)
- Though epigenetic expression decreases with age, it is never zero. Therefore, environmental issues do matter.

Medical Factors in Obesity

- Aside from Genetic and epigenetic causes already discussed, Obesity can have medical causes, including iatrogenic causes.
- Endocrine dysfunction, including but not limited to hypothyroid, diabetes, hypopituitarism, cortisol disorders, and others, are each important in their own right, but exceed the scope of this presentation.
 - For your patient, an appropriate workup for these conditions is warranted, as the patient's history dictates. For many of these conditions, we have widely accepted diagnosis and treatment protocols.
- OSA, sleep deprivation, are also significant exacerbating factors in obesity.

Medical Factors in Obesity

While Obstructive Sleep Apnea (OSA), is sometimes caused (or exacerbated) by increased adipose deposition, particularly in the neck area, it also can cause increased body weight.

The mechanism of this is believed to be due to metabolic dysregulation, pro inflammatory markers, and endogenous cortisol dysregulation.

Diagnosing and managing OSA is important in any treatment plan for increased body habitus, a topic worthy again of its own separate presentation.

It should be noted, that sleep deprivation can exist separate from OSA, such as shift work sleep disorder.

(Romero-Corral, 2010)



Iatrogenic Causes of Obesity

We as physicians, and the medical system in general are often a contributing factor of increased body habitus. Various medications (and other treatments) cause weight gain. They may include(but are not limited to):

Kyle, Kuehl, (2022) - this series of 5 slides

Drug Class/Type (and Potential Related Weight Gain)	Common Name	Proprietary or Brand Name	Alternative Drugs (Weight neutral or may promote weight-loss)
Diabetes Therapies (may cau	se up to 8 kg weight gain in an i	ntensive 3-month treatment co	urse)
Insulin	insulin lispro insulin aspart insulin glulisine	Humalog° Novolog° Apidra°	metformin (Glucophage°, Glucophage° XR, Fortamet°, Glumetza°, Riomet°, generics)
Thiazolidinediones (TZDs)	pioglitazone	Actos [®]	Linagliptin (Tradjenta®) saxagliptin (Onglyza®) sitagliptin (Januvia®) exenatide(Byetta®)
Sulfonylureas (SUs) usually ≤5 kg gain during 3-12 months of treatment	glipizide glyburide glimepiride chlorpropamide tolbutamide	Glucotrol® Glucotrol® XL Diabeta® Micronase® Glynase® Amaryl®` Diabinese® generics	Liraglutide (Victoza [®]) acarbose (Prandase [®] , Precose [®]) miglitol (Glyset [®]) <i>These combination products tend to have fewer</i> <i>side-effects and less weight gain:</i> metformin/pioglitazone (Actoplus Met [®]) glipizide/metformin (Metaglip [®]) glyburide/metformin (Glucovance [®]) glimepiride

Iatrogenic Causes of Obesity

The list presented over these 5 slides is not exhaustive, but rather a introductory look at iatrogenic causes.

Psychiatric/Neurologic Therapies

Tricyclic Antidepressants General gains of 0.4 to 4.12 kg/month minority of pa- tients gain 15 to 20 kg in 2 to 6 months	amitriptyline doxepin imipramine nortriptyline trimipramine mirtazapine	Elavil* Endep* Vanatrip* Adapin* Dilenor* Sinequan* Tofranil* PM Aventyl* Pamelor* Surmontil* Remeron* Remeron* SolTab*	Buproprion (Aplenzin®, Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®*, Zyban®*) *Black Box warning for increased risk of seizure. nefazodone (generics†) †Black Box warn- ing for liver failure and suicidal thoughts.
Selective Serotonin Reup- take Inhibitors (SSRIs) Initial weight-loss followed by gain within 6 months in a minority of patients	sertraline paroxetine fluvoxamine	Zoloft" Paxil", Paxil" CR, Pexeva" Luvox", Luvox" CR	
Lithium Gains in 11% to 65% of treated patients; up to 10 kg or more in 6 to 10 years		Eskalith°, Eskalith CR°, Lithobid°	

Iatrogenic Causes of Obesity

Antisychotics (most likely to cause weight gain)			
	haloperidol loxapine clozapine chlorpromazine fluphenazine risperidone olanzapine quetiapine	generics Oxilapine [®] , generics Clozaril [®] , FazaClo [®] Thorazine [®] generics Risperdal [®] , Risperdal [®] M-TAB [®] Zyprexa [®] Seroquel [®] , Seroquel [®] XR	Ziprasidone (Geodon*)
Antiseizure/anticonvulsa	ints		
Variable gains of up to 15 to 20 kg	valproic acid (sodium valproate, divalporex sodium)	Depakote° Depakene° Depakote° ER Depakote° Sprinkle Stavzor°	topiramate (Topamax®) zonisamide (Zonegran®) lamotrigine (Lamictal®‡) ‡ Black Box warning for serious rash.
Gains of up to 15 kg during 3 months of treatment	carbamazepine	Carbatrol° Epitol° Equetro° Tegretol° Tegretol° -XR	
	gabapentin	Horizant [®] Neurontin [®]	

Iatrogenic Causes of Obesity

Steroid Hormones			
Oral Corticosteroids (used to treat systemic anti-inflammatory diseases) Polymyalgia rheumatica: 2 to 13 kg Gains in >50% patients receiving 1 year daily prednisone	prednisone cortisone	Prednisone Intensol® Sterapred® Sterapred® DS	NSAIDs (where appropriate)
Inhaled Corticosteroids (used to treat asthma)	budesonide ciclesonide fluticasone	Pulmicort® Alvesco® Flovent®	
Hormone Therapy/ Contraception hormone therapy (used to treat menopausal symptoms and contraceptive agents to prevent pregnancy)	estrogen progestagens		

Iatrogenic causes of Obesity

Miscellaneous Agents diphenhydramine Aler-Drvl® decongestants and inhalers Antihistamines **Benadryl**[®] (Taken for sleep in patients Diphenhist[®] affected by obesity, Nytol[®] Benadryl^{*} can mask sleep PediaCare Chilapnea; also used as allergy dren's Allergy® medication) Siladryl® Silphen® Sominex[®] Unisom[®] generics propranolol Inderal[®] ACE Inhibitors: **Beta-Adrenergic Blockers** Inderal[®] LA ramipril (Altace°+) (used to lower blood InnoPran[®] benazepril (Lotensin°+) pressure) InnoPran[®] XL enalapril (Vasotec*+) Pronol® lisinopril (Prinivil°+, Zestril°+) Lopressor[®] metoprolol Angiotensin II Receptor Blockers: **Toprol**[®] losartan (Cozaar®+) Toprol XL[®] candesartan (Atacand®+) atenolol + Black Box warning for use during pregnancy Tenormin[®] Ca⁺⁺ Channel Blockers

(Kyle, T., Kuehl, B. 2022, this and previous 4 slides)

There are a myriad of social and cultural factors or pressures that are placed on everyone, every day. From the APA, Socio-cultural is defined as such:

"environmental conditions that play a part in healthy and adaptive behavior and well-being or in maladaptive behavior and the etiology of mental disorder and social pathology. Examples of sociocultural factors of a positive nature are a <u>strong sense of family and community support and mentorship, good education</u> <u>and health care, availability of recreational facilities, and exposure to the arts.</u> Examples of a negative nature are <u>slum conditions, poverty, extreme or</u> <u>restrictive occupational pressures, lack of good medical care, and inadequate</u> <u>educational opportunities." (American Psychological Association, 2021)</u>

Each of the previously listed causes can affect body habitus, but just as an example:

Regular white bread cost: \$0.99 (20 oz.)

Keto low carb bread cost: \$4.99 (14 oz.)

Little Caesar's Hot n Ready Pizza cost: \$6.00

From this, you can see how when finances are tight, it is difficult to eat in a healthy way. And, this is just one example.

(Prices are from Meijer.com and LittleCaesars.com retrieved on 19 Aug 2021)

Other larger more specific sociological factors contribute to increased body habitus. They include (just to name a few):

Now discredited research on low fat diets that was funded by the sugar industry (Domonoske, C, 2016) and as an example, and a selection of other influences from food production entities.

The BMI threshold for obesity was changed (lowered) in 1998. 20% of the population became obese overnight, very possibly secondary to lobbying by those invested in weight loss products.(CNN.com, 1998).

The weight loss industry reached a value of 78 billion in 2019 (yahoo.com 2021), Herbalife, which has a weight loss product, spent 2 million in lobbying alone in 2013(cnbc.com, 2014) Less honest actors in the weight loss industry may depend on repeat business to some extent. This creates a significant bias, for their lobbying efforts.

"I'll never willingly go to see a doctor ever again..." (de-identified person of size)

Sometimes physicians and the medical field contribute to sociocultural factors that exacerbate obesity. For example:

- "...To assess sources of possible weight stigma, participants were provided a list of 22 types of individuals, ranging from spouses to servers at restaurants...In fact, <u>over half of the sample reported that they had experienced "inappropriate" comments from doctors</u> regarding their weight at some point in their lives."
- "In another study, 24 percent of nurses reported that they felt "repulsed" by patients who were obese and 12 percent reported that they did not want to touch these patients..."
- "...79 percent of facilities did not have gowns sized for larger patients, more than half did not have armless chairs, and 40 percent did not have exam tables that could accommodate a patient who was obese..."

(Schvey, 2010)

"I've never felt more humiliated than after my last encounter with a doctor..." (de-identified person of size)

What can you do as a physician to address socio-cultural factors?

- Recognize a person's dignity as a human being, regardless their size.
- Educate as best as you can, but understand that patients may not be able to comply, or that it may be very difficult to comply.
- Connect patients with as many resources as possible.
- Encourage exposure to the arts, and finding physical activities that enrich a patient's life.
- Ensure that your exam room (or wherever you practice) is a non-judgmental space, where patients feel comfortable and supported by you and the setting.
- Advocate for your patients. You may be the only support they have.
- Advocate for improvement of population health issues that treat increased body weight in an unbiased fashion.
- Do not, as physicians, contribute to this problem, if at all possible.

Psychological Factors in Obesity

Eating, sleeping, exercise, are all behaviors. And, behaviors can be influenced significantly by psychological factors. This can be indirect, for example:

In a patient that suffers from depression, how likely is it that they can maintain an exercise routine?

It is important to remember, that **nearly every person of size you treat, has a traumatic history**. Abuse, bullying, job loss, romantic difficulties, mistreatment by the medical field are the **norm** in this group.

- From Schvey(2010), "Individuals who have been stigmatized due to their weight report increased vulnerability to depression, anxiety, body image disturbance, binge eating, decreased self-esteem, and suicidality"
- Even if psychological factors were not part of the genesis of the patient's increased body weight, they are at least likely to be contributing to the diagnosis.

Psychological Factors in Obesity

There are more direct psychological factors as well, such as binge eating disorder as just one example.

Binge Eating Disorder:

The key diagnostic features of BED are:

- 1. Recurrent and persistent episodes of binge eating
- 2. Binge eating episodes are associated with three (or more) of the following:
 - Eating much more rapidly than normal
 - Eating until feeling uncomfortably full
 - Eating large amounts of food when not feeling physically hungry
 - Eating alone because of being embarrassed by how much one is eating
 - Feeling disgusted with oneself, depressed, or very guilty after overeating
- 3. Marked distress regarding binge eating
- 4. Absence of regular compensatory behaviors (such as purging).



(nationaleatingdisorders.org, 2021)(Acaciadreams.co.uk, 2022)

Psychological Factors in Obesity

Treatment of Binge-eating disorder and other psychological factors should be undertaken, prior to treatment specific for increased body weight. Treatment modalities might include CBT, lisdexamphetamine, Antidepressants (usually SSRI's or SNRI's).

Keep in mind, this is just <u>one example</u> of a direct psychological factor. There are many other psychological conditions, which contribute to, or are exacerbated by increased body weight. Diagnose and treat these, as part of your treatment of increased body weight.

Gut Microbiota and Obesity

Recent Research has suggested that the gut microbiota have a significant role in the continuum of body habitus

"Recent evidence suggests that the trillions of bacteria that normally reside within the human gastrointestinal tract, collectively referred to as the gut microbiota, affect nutrient acquisition and energy regulation; it further suggests that obese and lean people have different gut microbiota. These findings raise the possibility that the <u>gut microbiota has an important role in regulating weight</u> and may be partly responsible for the development of obesity in some people. This article examines the evidence supporting these claims and explores whether modifying the gut microbiota could one day be a treatment option for obesity." (DeBaise et al, 2008)

Gut Microbiota and Obesity

"Jeffrey I. Gordon and his team have initially proposed that the gut microbiota was a key factor involved in energy storage and fat mass gain. They discovered that germ-free mice (i.e., axenic, without microorganisms) were gaining less body weight and fat mass than mice harboring a gut microbiota (i.e., conventional mice) [4]. In a follow-up study, they provided the proof of concept by showing that germ-free mice were also resistant to high-fat diet-induced obesity, even if the rodents ingested the same amount of calories [5]." (Cani, Van Hul, 2020)

"Then, it was discovered that transferring the gut microbiota from obese subjects into germ-free mice partially replicated the increased body weight and fat mass gain, thereby suggesting a causality between the microbiota and obesity [7]." (Cani, Van Hul, 2020)

"More strikingly, the collected data also pointed out that several other phyla or even specific bacteria were also affected by obesity or leanness. This is for example the case of well-known Actinobacteria such as *Bifidobacterium* and of the Verrucomicrobia representative *Akkermansia muciniphila* [9]" (Cani, Van Hul, 2020)

Gut Microbiota in Obesity

There are many articles on this topic, and surely more to come, but we are seeing our first forays into treatment based on this science(for now, specific to DM2).

In particular, a new product containing Akkermansia Muciniphila is now available:

(image from Pendulumlife.com, 2021)



Gut Microbiota in Obesity

"The large majority of microbiome colonization occurs in the early years of life. This topic has been reviewed extensively. During and shortly after birth, newborns are exposed to maternal and environmental microbes initiating gut microbiome establishment. Within the first year of life, an estimated 10^13 to 10^14 microbes/ml comprising 500–1000 species colonize the gastrointestinal tract. After weaning, the gut microbiota becomes firmly established, leading to a lifelong microbiome signature in healthy individuals...An especially interesting area of research is the increasing evidence that antibiotics in early life have a profound effect of the gut microbiome that can result in the later development of obesity, asthma, inflammatory bowel disease and other disorders." (Gilbert et al 2021)

Although it is possible to nudge the microbiota, major intentional change to it is elusive. A significant portion of your microbiome is set early in life. This has significant implications. Mouse studies mentioned previously, do show that a change in microbiota can make a difference, or that it is possible to change. And we see that that is the case with the successes of fecal transplants. However, our base microbiome forms early on in life, probably starting in our first hours of life, and our immune system forms around this and participates in its maintenance, even if it is dysbiotic. Keep in mind, if a parent's biome is disrupted, they will/may pass this disrupted biome on to their children.

Gut Microbiota in Obesity

The role of antibiotics in the continuum of body habitus:

"Treatment with ciprofloxacin influenced the abundance of about one third of bacterial taxa in faecal samples. These changes decreased the taxonomic richness, diversity and evenness of the community. Although most bacterial groups recovered after treatment, several taxa did not (even after six months) and the level of reconstitution varied between the individuals." (Cully, 2019)

- So, in short, antibiotics permanently change your gut microbiota.
- "In this study, repeated antibiotic exposure in early childhood was associated with higher mean BMI-for-age z score and an increased likelihood of obesity." (Chelimo, et al, 2020)
- Though there is much we do not know, it is reasonable to be cautious with antibiotics prescriptions.
 In addition, probiotics may be used to help counteract this, though research so far does not reach consensus(that I know of).

Particularly, the patient's diet, and their physical activity.

- These are the most modifiable factors. This is what can be changed, so we focus on these, but do not forget that they exist in the context of all the other factors previously discussed.
- It is sometimes easy for us to conceptualize lifestyle change, but remember, many other factors may make this difficult. In other words, the patient's locus of control may not be as substantial as you may assume. It is an implicit bias, if we believe a patient's locus of control is larger than it is.

- Set realistic goals that are directly measurable and achievable. Your goal for your patients should be the behavior change, not their weight, except in specific circumstances.
 - When you focus on weight, this is a secondary endpoint. Patients may make good lifestyle changes, and not lose any weight due to non-modifiable factors. This leads to frustration and feeling of the weight being "out of their control." Focusing on the behaviors themselves, as a primary endpoint, is more likely to lead to a feeling of success or progress for the patient and empowers them.
 - For example: <u>"What I'd like you to do, is find a physical activity you enjoy</u> doing, and make sure you do it every day. I'd like to see 30 minutes of that activity every day. You may not lose weight, especially at first, but every day you meet this goal, is one day of healthier living, and that is worth celebrating."

- Encourage regular monitoring of behaviors such as intake, exercise, attendance at counseling, initiation of new non-food behaviors , and infrequent monitoring of weight.
- A patient's weight is often used as a quality measure, based primarily on their easy to acquire and objective nature. Focusing too closely on these measures is not excellent care.
- Shame and/or fear are not accepted methods for motivating meaningful behavioral change in any situation, and serve to exacerbate trauma, as we know from models such as the Adverse Childhood Events (ACE) model. They actually serve to increase the likelihood of problematic coping behaviors, do not assist in achieving the goal of weight reduction and may lead to increased body habitus. (Schvey, 2010)

- Modification of lifestyle factors probably doesn't cause weight loss just based on "Calories in vs. calories out". There are many areas of research regarding this, and data is preliminary.
- It seems that the mechanism for loss of weight has as much to do with improving the normal functions of adipose tissue, and also enacting changes in microbiota and genetic/epigenetic expression.

The Intersection of Implicit Bias and Obesity

- Implicit and explicit bias does in fact exist against persons of size, and it is measurable. This is real!
- In one study, the implicit and explicit bias preferences regarding body weight, were stronger in comparison to biases against race, skin tone and ethnicity by the conclusion of the longitudinal study(Charlesworth, T., Banaji, M, 2019)
- Implicit and explicit bias against body size has been socio-culturally acceptable.
 This may mean people were more honest in their surveys regarding this.
- Over a period of 10 years, implicit and explicit biases on body weight changed the least compared to other biases, including disability, age, skin tone, sexuality and race. In fact of the areas studied, they were the only category that trended away from neutrality. (Charlesworth, T., Banaji, M, 2019)
- Bias regarding body weight needs to change!

- Start with recognizing and acknowledging your own biases regarding body weight.
- Acknowledge for yourself and for your patients, that increased body weight is not a personal failure.
 - Set aside the assumption that the patient has just "decided" to be a person of size. Most, but not all patients to have elevated body weight, and most but not all would not willingly make choices towards this.
 - There are those patients who have fought for healing of trauma, and have done so through body size acceptance. This is a topic that deserves its own lecture as well, but in short, we must respect the right of patients to live their own truth. This does not prevent us from addressing primary goals for healthier living.

- A change in perspective goes a long way in mitigating bias.
 - Imagine the patient's chief complaint, and then ask yourself how you might manage this, if they had a normal BMI.
 - How would you manage a patient with Asthma and normal BMI? Can you manage a patient with asthma and increased body habitus similarly?
 - Take a practical but unbiased, non-judgmental approach
 - . If the patient doesn't come back to the clinic, you cannot help them.

- Acknowledge that you respect the patient and will treat them with dignity.
 Tell this to the patient. Say it out loud.
 - One resource for understanding how to do these things, is the "Health at Every Size (HAES) movement. A website with more information is:
 - asdah.org/health-at-every-size-haes-approach. (Penny, T., Kirk, S., 2015)
 - HAES focuses on the following principles:
 - Weight inclusivity,
 - Health Enhancement,
 - Eating for Well Being,
 - Respectful Care,
 - Life Enhancing Movement (ASDAH.org, 2021).

"I have had knee pain for one and a half years, and you are the first physician that has addressed this other than telling me to lose weight..." (de-identified person of size)

- Educate the patient about factors that contribute to increased body weight as a disease.
 - Use words that acknowledge the health problems increased body weight increases their risk for, but also acknowledge their worth and dignity as a human being. For example:
 - "People come in all shapes and sizes, and we are all still entitled to dignity. However, those of us that carry extra weight, may put additional strain on our spines."

Plan for recurrent visits, as this is a key part of management of any chronic condition. For that to happen, patients must be comfortable with returning to your clinic. You can ensure that your clinic is welcoming to larger people:



- Ensure waiting area and exam rooms do not have hostile architecture

- Wide bench seating as part of a variety of seating options, seating of various heights, wide aisles and doorways.
- Adjustable height exam tables (so they can be low for patients to get on, then be raised up)

"I do not trust doctors..." (de-identified patient of size)

Plan for recurrent visits, as this is a key part of management of any chronic condition. For that to happen, patients must be comfortable with returning to your clinic. You can ensure that your clinic is welcoming to larger people:

- Ask for <u>consent</u> to discuss weight issues, and only discuss after primary concern is addressed. Consent each step of the way helps to build trust.
- Avoid weighing patients routinely.
 - Appropriate to do if medically necessary, but ask for <u>consent(physician or staff)</u>
 - Offer patients "no weigh" cards, or build this into their chart: <u>https://more-love.org/free-dont-weigh-me-cards/</u>
 - Balance your quality measures with this. I suspect, the overall quality measures will be better for a patient that isn't weighed, but trusts you, and returns to clinic regularly).

 Treatment for increased body weight should exist in conjunction with therapies aimed at behavior change(primary result). Counsel patients about establishing new habits. This can be done even in patients who do not desire to lose weight.

- As possible, evaluate for and treat for other factors in that may be contributing to or exacerbated by increased body weight.

- This includes but is not limited to medical causes. Be systematic but also non-judgmental.

Kahan and Manson(2019) suggest the acronym ABCDEF:

Table. An "ABCDEF" Approach to Guide Weight Counseling in Primary Care

Steps	What to Do
Ask "permission"	 Assess patient readiness to discuss weight issues. Consider begining the conversation with questions such as, "Your weight has been increasing over the years, which could lead to diabetes and other health problems. Would it be okay if we started working together on this?"
Be systematic in the clinical workup	 Elicit weight history, motivations, barriers, and social determinants. Medications that may cause weight gain include some antidepressants, antipsychotics, insulin, sulfonylureas, steroids, and pain medications.
Counseling and support	 A wide range of dietary patterns can help weight management. Physical activity, even just walking, is essential for health. Use free online tools and resources, such as Dietary Guidelines for Americans, obesity treatment guidelines, and the Diabetes Prevention Program curriculum and handouts.
Determine health status	• Evaluate for weight-related health conditions (eg, diabetes, sleep apnea), physical limitations, and decreased quality of life.
Escalate treatment when appropriate	 Consider medication (BMI ≥27) or bariatric surgery (BMI ≥35) when weight-related health conditions are present. Medication options for long-term use include orlistat, lorcaserin, phentermine/topiramate-extended release, naltrexone/bupropion-sustained release, and liraglutide.
Follow up regularly and leverage available resources	 Create a care team by identifying local obesity specialists (eg, obesity medicine physicians, registered dietitians), community programs (eg, YMCA-based diabetes prevention program), and other resources (eg, commercial weight-loss programs, health coaches, digital or telehealth platforms). A few minutes at the end of an unrelated appointment can be used to check in on patients' progress and offer support. Utilize medical assistants and other office staff to save time by assisting with patient education, monitoring, and coordinating car

Prevention is always the best medicine:

The path toward increased body weight begins with conception (or maybe even before conception). Ensuring your pregnant patient has a healthy pregnancy is an important start. Once the child is born, or even before birth, you should begin to counsel the parents about healthy eating habits, focused on behaviors, while validating self worth. If a person is trying to conceive, they should ideally be on prenatal vitamins, folic acid(or L-Methylfolate), and one should consider vitamin D, and a high antioxidant diet.

Screen time is one example of several behavioral factors in elevated BMI in children. This also warrants its own separate lecture, A focus on behavioral change early will be beneficial but should recognize the dignity of the patient and the parents of the patient still applies.

Children need to try food multiple times, perhaps as much as 10-14 times, before they will like it (Wardle, et al 2003). Your role is to help parents understand that in all things, behavioral change takes time. We all often fail to acknowledge how much diligence it requires to change a behavior.

Obesity Treatment

General Recommendations:

- Prevention is the best medicine.
- ALL intervention that address increased body weight should be used in conjunction with therapies aimed at behavior modification. Counsel patients and parents about establishing new habits while on these medications. Remember, it can help to focus on primary goals, not secondary goals such as weight loss.
 - Involve dietitian or counseling when possible.
 - Address diet interventions, such as food selection and portion control.
 - Encourage behaviors that reduce oxidative stress for those that wish to become parents.
 - Nutrition and behavioral counseling is a separately billable CPT code, that can be used with patients with elevated BMI's (cpt code 99401)
 - Encourage life enhancing movements and activities (music performance, Sports, Theatre, etc.)
 - Minimize antibiotic use

For the longest time, we have had no medications that were safe and effective. Phen-fen was pulled off the market, after it caused heart issues, and Meridia(sibutramine hydrochloride monohydrate) had an extensive side effect profile and is no longer available, for the most part. Lorcaserin was also pulled from the market recently, after exposure was linked to increased cancer rates. Most of these medications helped with weight loss <u>at the expense of overall health.</u>

As understanding of the physiology of the continuum of body habitus has progressed, we have for the first time, a relatively safe and effective drug class. These are the GLP-1 medications.

GLP-1 Stands for Glucagon like peptide. It mimics a peptide hormone that is released when the stomach signals fullness with stretch receptors, causing a release of insulin, along with a feeling satiety.

- **Saxenda** (liraglutide, basically same as Victoza but higher dose) can be used with significant effect.
- On June 4th, 2021, the FDA approved **Wegovy** (Semaglutide, same as Ozempic, but higher dose), for weight loss (FDA.gov, 2021), but though not all are approved, likely all GLP-1's cause weight loss.
- Many GLP-1 medications have evidence of reduced cardiovascular health events, and are the first class of medications for treatment of elevated BMI to show this in studies. (novomedlink.com, 2021).
 - This means that the medication improves health, while decreasing weight an important feature of these medications that has not previously been demonstrable with other medications.
- Certain people with a risk of rare, genetic cancers should not take GLP-1's (Thyroid cancer, MEN2 mutation, a risk that very rare, theoretical)
- Similar to blood pressure medications, these medications may need to be continued for long periods. There can be regain when they are stopped.
- GLP-1 medications are non-habit forming, and are not controlled substances.

GLP-1 +GIP

- In addition to GLP-1, other peptide hormones are released when the stomach is full. GIP, which stands for glucose insulinotropic Peptide, mimics one endogenous peptide. Currently Tirzepatide (Brand name Mounjaro) is the only medication that contains both of these.
- Tirzepatide was approved for treatment of Type 2 Diabetes on May 13, 2022. It is NOT currently approved for weight loss, however, industry experts have alluded that it will be soon. (<u>https://www.fda.gov</u>, 2022)
- Long term data on cardiovascular effects are not yet done, but given similarities to GLP-1 only medications, a positive effect is at least plausible.

Pharmacological management is rapidly progressing! There are no less than 15 medications targeting various proteins or genes in the pathways of body habitus continuum working their way through FDA approval(clinicaltrials.gov, Won Son, J., Kim, S., 2020)

- Two to look out for are:
 - NNC9204-1706 A which is listed as a GLP-1R/GCGR/GIPR triple agonist by some sources (Won Son, J., Kim, S., 2020)
 - NNC9204-1177 or JNJ-64565111 which are listed as Dual GLP-1R/GCGR agonists (Won Son, J., Kim, S., 2020)
 - A wide variety of medications, each targeting different genetic targets/ mechanisms for increased body habitus

Wellbutrin (Bupropion**)** and **Naltrexone** (available in a single pill called **Contrave**) - this combination of medications works to address psychological factors and reduce craving. **Contrave** is often not covered by insurance, but the separate medications can be prescribed with good coverage typically(<u>www.drugs.com</u>, 2021, Early, Whitten, 2015).

Adipex (phentermine) is also available still, and can be used short term, typically 6-12 weeks. It has significant side effects, and risks. It is a stimulant medication, and has a similar effect of appetite suppression like Adderall does. A Phentermine/Topiramate combo medication is also available with reasonable evidence(Won Son, J., Kim, S., 2020). Individual medications can be used separately off-label for similar effect. The same cautions apply to the dual medication as to Adipex alone. Topiramate can suppress appetite as well, but by a different mechanism(antagonizes glutamate receptors, augments GABA-A receptors).

Olestra, available under brands **Alli, Xenical**, and **Orlistat** are also available, but are poorly tolerated and used relatively rarely.

Surgical Treatments for Obesity

There are surgical options, which include a suite of gastric bypass, sleeve, and various other procedures. This is a large topic that also warrants its own lecture. However, as a physician, you should work on the medical and behavioral changes as a first line, as they are crucial, whether your patient has surgery or not. You can help lay the groundwork for successful surgical intervention.

Surgical options carry risk, at least as much as any surgery, but also patients with increased body weight may be at higher risk for any surgery. In addition, post-surgery, there can be numerous long term health complications, an important topic that warrants a lecture of its own as well. I will leave further discussion of the specifics to the surgeons that specialize in this. I will point out, however, that surgical techniques and equipment have improved dramatically over the past 20 years, and as a result, outcomes are better.

Surgical Treatment for Obesity

Preparing for Bariatric Surgery

- GLP-1 and GLP-1/GIP medications should be attempted prior to surgery if possible. For some, weight loss may be nearly as effective as gastric bypass, and this can help them prepare for the intervention.
- Keeping a food diary and an exercise log is sometimes required prior to gastric bypass surgery. It is also a helpful tool for patients to gain insight into how disordered their behaviors are. Use this cautiously, as this can descend into eating disorder territory for some patients.

Summary

Obesity is a multifactorial, chronic condition.

Those who struggle with increased body weight are burdened with past and present discrimination and stigma. You can be a powerful part in changing this stigma.

Treatment should be non-judgmental, multimodal, with a focus on primary endpoints, while avoiding focus on secondary endpoints when possible.

A patient has the greatest success in managing their body weight, if they continue to come to see you! Creating a safe environment will increase the likelihood that patients will return to you.

There are now many successful pharmacological and surgical treatments for increased body weight, and there will likely be many more in the future.

Questions and Discussion?

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What questions or discussion points do you have?

Posttest

This is the conclusion of the lecture. At this point, you should take the posttest, which should come as a pop-up of some form. Remember, this must be completed to receive implicit bias credit with the State of Michigan.

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