PANHANDLE HEALTH

A QUARTERLY PUBLICATION OF THE POTTER-RANDALL COUNTY MEDICAL SOCIETY SPRING 2026 | VOL 36 | NO.2

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PANHANDLE HEALTH

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Executive Director's Message

by Katt Massey, Executive Director, Potter-Randall County Medical Society

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A quick survey that will help us improve your PHM experience!
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Hello PRCMS Members and Beyond,

The first time I remember being on "a diet" was in 1996. I was in the 6th grade. My mom made me "Adkins" low-carb meals to take to school. At that age, I never really saw myself as "big." I was just me. I've been on every diet since. I've even considered surgery. And now there are pills. Legit magic.

I remember doctors being brash and harping on my weight so much so that I'd resent them. I would note to all of them, "besides my weight, I am healthy." When we were trying to have children, a fertility doctor in Dallas (I'll never forget him) tried to diagnose me with PCOS. "A rare form" he said…just because I was overweight and not menstruating. I scoured all the paperwork my OBGYN had given me; I researched. My bloodwork was fine and my hormone levels were fine. I was so confused. This doctor treated me awfully. I've never really heard my husband yell at anyone, and he did that doctor. At the end of all the chaos of it, appointments, blood draws, a shot of who knows what... I looked at my OBGYN in tears and said, "I don't think I have PCOS," to which she replied, "You don't. You never did."

That doctor couldn't figure out why I wasn't menstruating; he just wanted to get me in and out and needed something to blame, and that was my weight. Turns out I'm a 1 percenter, the 1 percent of patients where the depot birth control shot didn't leave my body until a year after I stopped taking it. I am grateful for the next fertility doctor and the time he took to make sure I felt seen beyond my "chunk."

When the discussion of this issue came about, of course I got a little defensive. But when Dr. Biggs mentioned that it could be genetic…I was relieved. I've learned to love myself. It's taken a while, and no, healthy lifestyles are always at the top of mind. Someday I'll get there.

On a "lighter" note, lots of fun things are coming up. Expect a TEX Med update in the next issue. Make sure you mark your calendars for the 3rd Saturday of the month for Walk With A Doc. We're meeting at the PRCMS Building at 9:30 AM, and walking across the street to the park after the Doc Talk.

Soon,
Katt

EDITORS NOTE:

The Panhandle Health Editorial Board would like to share their apologies for the misprint of Brittany Taute, M.D's photo.

Her article in the Winter 2026 Issue "Ringing in the New Year," was:
A History of Inpatient Hospice Care in Amarillo: From Sister Olivia & Dr. Gerry Holman to the New Inpatient Unit at BSA by Brittany Taute, MD and Randy Stewart, MD, FACP, Medial Directors, BSA Hospice of the Southwest.

Dr. Brittany Taute MD

is a Tascosa grad (Go Rebels!) who studied Business Management at WTAMU and then went on to medical school at UTMB in Galveston, from which she graduated in 2015. Dr. Taute completed her residency in Family Medicine at TTUSOM in Amarillo and joined the BSA Hospitalist group in 2018. In 2021 she joined BSA Hospice of the Southwest in 2021 and now works on the hospice inpatient unit as well as the inpatient ward service at BSA.

President's Message

by Ryan McKenna MD, MBA

Please allow me to introduce myself. I am Dr. McKenna, an Interventional Pain Physician and Anesthesiologist with deep roots in West Texas, having grown up in Midland. My family and I have called Amarillo home for the past six years, and we cannot praise this city enough for its family-friendly lifestyle and its outstanding medical community. It is a great honor to be writing my first President's Message for Panhandle Health.

This spring issue focuses on a topic that some may consider mundane: obesity. However, this ubiquitous and complex health problem has a fascinating history, and has been a health scourge for decades. Indeed, for the past 50 years, it has seemed that the one who created the elusive cure for obesity would be rewarded with fame, fortune, and lasting societal influence.

Obesity is not a modern phenomenon. Archaeological evidence includes figurines depicting obesity dating back to the Stone Age, between 230,0000 and 35,000 years ago. Obesity has been depicted across multiple ancient and modern historic cultures including Greco-Roman, Byzantine, and Persian cultures, with many artistic depictions during the European Renaissance. What is interesting about obesity during this time is the defiance of the natural order of human existence. Humans in the distant past lived in a time of scarcity which required physical strength and endurance to survive. It is of no surprise that, during this time, the rare instance of obesity was regarded as symbol of status, beauty, fertility, and wealth.

Currently, the public perception of obesity has transformed into a stigmatized health issue including societal judgements on willpower, discipline, and intelligence. This can translate into real consequences for those affected in the settings of healthcare, workplace, and even social gatherings. Furthermore, obesity is associated with serious health conditions, accounting for numerous co-morbidities. The economic impacts include direct US healthcare system costs of $170 billion per year. Obesity also affects national defense, with estimates suggesting that only 2 in 5 young adults are eligible for basic training based on weight and physical conditioning requirements. There are social and behavior factors that coexist with obesity, which include unemployment, excessive drinking, smoking, lack of post-secondary education, and single parent households.

According to the CDC, the prevalence of obesity among adults is an amazing 40.3% as of 2023, and the prevalence of severe obesity in adults is 9.4%. The good news is that the prevalence seems to be stabilizing, as there was no significant increase from the prior decade. The list of co-morbidities of obesity is lengthy, including metabolic disorders such as type 2 diabetes, cardiovascular disease, non-alcoholic fatty liver disease, obstructive sleep apnea, osteoarthritis, and increased cancer risk for breast, colorectal, esophageal, kidney, pancreatic and liver cancers. In addition, there is an association with depression and anxiety. Furthermore, obesity can affect fertility due to its association with polycystic ovary syndrome.

In this issue of Panhandle Health, we will discuss a broad spectrum of ways to manage obesity. We will go over practical management of obesity and discuss psychiatric aspects of the disease. We will discuss specific issues related to women's health and obesity and how to manage the disease in those who are resource limited. We will also take an in-depth look at the nuances of bariatric surgery, what it entails, and who might benefit from consideration of surgical techniques. Finally, we will, of course, discuss the brave new world of GLP-1s and what that means for the future of weight management.

We hope you enjoy this issue and find that it provides some practical medical information regarding management of obesity. Of course, the interesting questions will remain, such as what the future holds. Who will have access to these amazing new weight loss pharmaceuticals? When will the prices become affordable to the population at large? Why do insurance companies refuse to pay for these drugs which, while expensive, will certainly decrease a person's lifetime healthcare costs? It will be interesting to see how this will play out, but hopefully a meaningful reduction in the prevalence of obesity is in the not-too-distant future.

Our Next Issue Of
Panhandle Health
Features:
Diagnostic Imaging and Beyond

Message from the Potter-Randall County Medical Alliance

by Alena Martin & Madeline Lennard, Co-Presidents

Wine Dinner 2026 was a resounding success! Our alliance was glad to host the current TMAA President, Joi Smith, as well as Lydia Soldano, TMAA president-elect. Both ladies enjoyed the view from the Amarillo Club and were welcomed in true Panhandle fashion. Joi and Lydia could not say enough kind things about our members and are so glad to see the Potter-Randall Alliance thriving. Thank you to everyone who attended, and especially our sponsors. It was great to see so many new faces. For those of you who could not attend, we hope you will join us next year. It's a wonderful opportunity to enjoy a beautiful meal and a few laughs with friends and colleagues alike. What could be better?

Thank you to everyone who brought a friend and joined us for Pride, Prejudice, and Popcorn. Viewing the Jane Austen classic, on the big screen, in a private theatre was such a treat. We hope each of you can join us at our next membership event. Keep an eye on your email for updates.

Beautiful spring days have us looking forward to the upcoming Doctor's Day Celebration on March 28th with the medical society. Please join us for a night of family fun on the medical society lawn. You can be sure that the Alliance will be sponsoring something fun!


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Guest Editorial
GLP-1: The Most Important Metabolic Breakthrough Since Insulin?

by William C. Biggs, MD

We are witnessing a genuine inflection point in obesity and metabolic medicine: GLP 1–based therapies are producing weight loss and cardiometabolic benefits that, until recently, were achievable mostly through surgery. What makes this revolution even more remarkable is its origin story—spanning nearly a century from the early 'incretin' hypothesis to the molecular decoding of proglucagon, the identification of bioactive GLP 1, and the engineering of long acting receptor agonists that finally overcame native GLP 1's rapid degradation. This article traces that scientific chain—from bench discoveries to modern clinical outcomes—and explains why these medicines are changing what clinicians can realistically offer patients.

GLP-1 therapies represent not just another class of diabetes drugs, but the first pharmacologic tools to approach bariatric surgery in metabolic impact—while simultaneously reducing cardiovascular risk. That combination may ultimately redefine chronic disease management.

THE DISCOVERY AND CHARACTERIZATION OF INCRETINS

I was fortunate to be a fellow at Harvard Medical School and the Joslin Diabetes Center in the mid-1980's, working under Gordon Weir. Gordon was distinguished as an expert in insulin secretion and islet cell physiology. As part of our normal cross-town communications with the endocrinology program at Massachusetts General Hospital (MGH), we became aware of MGH's interest in incretins.

Incretins seemed to be hypothetical hormones at the time. Their existence was postulated by Jean La Barre in the 1930s, and confirmed in the 1960s by the fact that glucose given intravenously failed to increase insulin levels as robustly as the same glucose given orally. Something in the gut was signaling the pancreas to release insulin. Incretins are gut hormones that potentiate glucose dependent insulin secretion after meals; the only known candidate for an incretin in the 1970s was Glucose-Dependent Insulinotropic Polypeptide, or GIP.

An endocrinologist at MGH, Joel Habener, had a particular talent for finding the genetic basis for hormones and decided to work on the genetics of the glucagon gene. His lab cloned cDNA complementary to islet mRNA into bacteria to decode proglucagon and related peptides. City of Cambridge recombinant DNA rules required compliance with NIH containment/oversight, which made working with mammalian DNA difficult. Additionally, fishermen in Boston knew that anglerfish had an unusual feature where all of their islets were concentrated in pea-sized nodules rather than dispersed in tiny numbers throughout the entire pancreas. Thus, the original source of the proglucagon research was from fish, and specifically the anglerfish.

Habener was able to identify the proglucagon gene and found that it encoded not just glucagon but also two glucagon-like peptides, which were eventually labeled GLP-1 and GLP-2.

One of the most interesting features of this gene was that its final product – namely, glucagon or GLP-1 or GLP-2 - depended on the location of the cell. Different prohormone convertases (PC) drive tissue specific processing (pancreatic alpha cell PC2 → glucagon in α cells; intestinal L-cell PC1/3 → GLP 1 and GLP-2 in the intestine). Thus, cells in the pancreas produced glucagon whereas cells in the gut produced GLP-1.

Svetlana Mojsov in Habener's lab was able to synthesize these peptides. They shared them with Gordon Weir, whose Joslin lab had the ability to look at the response of the rat pancreas to various forms of GLP-1. Weir found that a truncated 31 amino acid (7-37) version was an extremely potent stimulator of insulin release and likely participated in the regulation of insulin release, partially fulfilling the definition of 'incretin' (1).

Dan Drucker, also in Habener's lab, was assigned to the incretin project. At MGH and later at the University of Toronto, Drucker identified the biological functions of GLP-1 in humans to include stimulation of insulin release, suppression of glucagon, and delayed gastric emptying. Additional early work on the human biology of GLP-1 was done at Novo Nordisk in Copenhagen by Jens Juul Holst, who showed that GLP-1 is secreted after meals and circulates in humans, confirming that GLP-1 was truly an 'incretin'.

However, despite these potent effects, native GLP 1 is rapidly inactivated within minutes by the enzyme DPP-4, limiting therapeutic use without modification. This made GLP-1 impractical for use as a therapy. We thought incretins such as GLP-1 were an interesting part of vertebrate physiology but unlikely to be very useful clinically.

DEVELOPING CLINICALLY USEFUL INCRETIN MIMETICS

At this point, John Eng enters the picture. He was a New York VA endocrinologist who trained under Rosalyn Yalow, who herself had won the Nobel Prize for

inventing the radioimmunoassay to measure insulin. Animal venoms were known to act in the pancreas to release amylase. Eng's lab was testing various reptile venoms to identify biological activity in the pancreas when he recognized there was a great deal of homology between a specific Gila monster venom called exendin-4 and GLP-1. He also determined that the half-life of exendin-4 was several hours, compared to a couple minutes for GLP-1. Since he was a VA employee, the VA owned the patent rights for any of his work, and the VA felt that Gila monster venom was so unlikely to benefit veterans' health that they didn't even want to fill out the patent paperwork. The VA declined to pursue patenting resources; Eng himself pursued development/licensing, leading to exenatide.

Eng's preliminary work was accepted as a poster at the 1996 American Diabetes Association meeting in San Francisco. A friend of mine, endocrinologist Alain Baron, was consulting for a small San Diego startup called Amylin and recognized the value of a prolonged GLP-1 agonist. Jens Juul Holst from Novo and scientists from Eli Lilly also took interest. Initially Eng wanted to sell his rights to exendin-4 to Eli Lilly, since his wife's name was Lily and since Eli Lilly was the predominant producer of insulin products in the USA. However, he found the negotiations there to be more like a job interview, so he went to his second choice Amylin to gauge their interest. He found that Amylin, which was struggling to get FDA approval on its launch product, Symlin, had an extremely high understanding of the GLP-1 potential and desperately wanted to get another product in its portfolio. Amylin licensed Eng's peptide technology in August 1996. Eli Lilly later assisted Amylin in developing and marketing the final product.

Exendin-4 was launched as exenatide (Byetta) in 2005 for treatment of diabetes. It was moderately successful, but its impact was limited by clinicians unfamiliar with dosing a product that had so many GI side effects such as nausea, vomiting, and diarrhea. It needed to be given two times a day by injection, and insurance coverage was sometimes difficult. Even so, exendin-4 was useful for some degree of weight reduction and for delaying the need for insulin in type 2 diabetes.

Holst and Lotte Bjerre Knudsen at Novo Nordisk were able to create new GLP-1 agonists with longer durations of action by changing amino acids to resist DPP4 degradation and by adding a long aliphatic carbon tail to promote albumin binding. The first iteration resulted in liraglutide (Victoza), which could be dosed daily and resulted in substantial improvement in glucose control along with weight loss.

Further refinements resulted in semaglutide (Ozempic / Wegovy) which allowed for weekly administration, and tirzepatide (Mounjaro / Zepbound) which co-activates GLP -1 and GIP.

PANHANDLE HEALTH

A PUBLICATION OF THE POTTER-RANDALL COUNTY MEDICAL SOCIETY

Editorial Policy and Information for Authors

Purpose: *Panhandle Health* strives to promote the health and welfare of the residents of Amarillo and The Texas Panhandle through the publication of practical informative papers on topics of general interest to most physicians while maintaining editorial integrity and newsworthiness.

Spectrum: The Journal seeks a wide range of review articles and original observations addressing clinical and non-clinical, social and public health, aspects as they relate to the advancement of the state of health in the Texas Panhandle. Pertinent letters to the editor, new submissions, and obituaries are accepted pending editorial review. The Editorial Board accepts or rejects submissions based on merit, appropriateness, and space availability.

Submission Process: Material should be emailed to katt.massey@prcms.com or mailed to Katt Massey, 1721 Hagy Blvd. Amarillo, Texas 79106. A recent photograph of the author (optional) and a curriculum vitae or biographical summary are also to be submitted.

Conflict of Interest: Authors must disclose any conflict of interest that may exist in relation to their submissions.

Journal Articles: Manuscripts should be double-spaced with ample margins. Text should be narrative with complete sentences and logical subheadings. The word count is generally 1200 to 1500 words. Review articles and original contributions should be accompanied by and abstract of no more that 150 words.

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References: References to scientific publications should be listed in numerical order at the end of the article with reference numbers placed in parentheses at appropriate points in text. The minimum acceptable data should include:

Journals: Authors, article title, journal, year volume, issues number, inclusive pages.
Books: Author, title, place of publication, publisher, year.
Websites: URL of the site and the date the information was accessed.

Other Sources: Enough information must be included so that the source can be Identified and retrieved. If not possible, the information for source should be included in parenthetically in the text.

Illustrations: Illustrations should be black and white only with complete-sentence legend.

Previously Published Material: Short verbatim quotations in the text may be used without permission but should be quoted exactly with source credited. Otherwise, permission should be obtained in writing from the publishers

Editing: Accepted manuscripts are edited in accordance with the *American Medical Association Manual of Style.*

Letters: Letters will be published at the discretion of the editor and editorial board. The length should be within 400 words. References should not exceed five. All letters are subject to editing and abridgement.

News: News should be emailed to katt.massey@prcms.com or mailed to Katt Massey, PRCMS 1721 Hagy Blvd. Amarillo, Texas 79106.

Obituaries: Listings of deceased members of PRCMS with highlights of their contributions are published with adequate information is availble.

Point of View: Opinions published in any article, statement, or advertisement are the responsibility of the author and shall not be construed by any means to represent those of the editors or the medical society.

In Amarillo, we have been participating in GLP-1 research for diabetes and weight management for the last 15 years, starting with liraglutide. Since then, we have had clinical trials with local patients using liraglutide, semaglutide, tirzepatide, cagrilintide, and survodutide, and we are preparing for additional trials with even newer agents such as zenagamtide. The most impactful of these trials has been the SELECT trial, which identified significant benefits beyond weight reduction, with a 19% reduction in all-cause mortality. A 9% reduction in cancer over 4 years did not reach a statistically significant level, but other GLP-1 products have similar cancer outcomes.

EFFICACY AND LONG-TERM BENEFITS OF THESE AGENTS--WILL A NOBEL PRIZE BE THE RESULT?

To say that these drugs are effective is an understatement. The newest products are seeing 20 to 30% or more weight reduction. Clinicians have become more skilled at gradually increasing the dose to minimize GI side effects. We have entered a phase of clinical research where the drugs are working so well that the patients are requesting a pause from treatment so that they and their families can adapt to the new lower weight. The recent REDEFINE Novo trial found that 43% of the subjects did not maximize the dose of their study drug. Interestingly those same 43% lost more weight than the subjects who took the full dose. Clearly the full potential of the new GLP-1 medications hasn't been established.

We are still only beginning to learn the multitude of benefits from incretin therapy beyond weight loss. Preliminary data suggest reductions in alcohol consumption, fatty liver disease, diabetic kidney disease, osteoarthritis, sleep apnea, inflammatory diseases, cardiovascular disease, and cancer. This will truly impact every aspect of medicine.

Many of us have had the opinion that something that works this well for weight loss and mortality reduction should result in a Nobel prize for its development. So far, no Nobel prize has been awarded despite such a clear indication. The informal opinion of the endocrinology community is that the award should have gone to Joel Habener for the discovery, Svetlana Mojsov for the peptide identification, Dan Drucker and Jens Juul Horst for human physiology, and possibly Lotte Bjerre Knudsen and John Eng for the drug development to a clinically useful product.

The Nobel Prize has not yet recognized the incretin discovery — perhaps because of the complexity of assigning credit across decades and continents. There also has been speculation that the Nobel committee was troubled by Dr. Habener's arrest for charges arising from a domestic dispute in 2005. He was later acquitted, although he was convicted of illegal possession of a firearm (2). He was placed on a leave of absence, and his patient care activities were restricted; he returned to research a year later. After a long career filled with amazingly creative work that spawned numerous researchers throughout the world and the creation of GLP-1 drugs, Joel Habener passed away last December at age 88.

Nobel Prizes are not awarded posthumously. The incretin revolution has saved lives, reduced suffering, and redefined chronic disease management. Few advances since insulin have had such sweeping impact. It would be difficult to imagine a more deserving candidate than GLP-1 for future Nobel recognition.

REFERENCES

1. Mojsov S, Weir GC, Habener JF. Insulinotropin: glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas. Journal of Clinical Investigation. Feb 1987; 79 (2): 616–619. doi:10.1172/JCI112855
2. New York Times. Joel Habener, whose research led to weight-loss drugs, dies at 88. January 9, 2026 https://www.nytimes.com/2026/01/09/health/joel-habener-dead.html

William C. (Reddy) Biggs has practiced medicine in Amarillo since 1986. He attended UT Southwestern in Dallas and completed his internal medicine residency at New England Deaconess Hospital and Harvard Medical School in Boston. He then completed a fellowship at Joslin Diabetes Center and Harvard Medical School. Dr. Biggs is a past president of the Texas Chapter of the American Association of Clinical Endocrinologists and has been an advisor to the AMA CPT Editorial panel. He is the Chief Medical Information Officer and Laboratory Director of Amarillo Medical Specialists, LLP and serves as CEO/Medical Director of the Amarillo Legacy Medical Accountable Care Organization. He is married to Emily Archer, MD; they have four children—two medical doctors and two attorneys!

The Pathogenesis of Obesity:
Or, Why are some people obese and others, not?

by Steve Urban, MD, MACP

INTRODUCTION

You will probably read a lot of statistics about obesity in this issue. Let me just mention a few:

1. Obesity is common. You can probably tell this by going to Wal-Mart, but the statistics back you up. Now, over 40% of women and almost that many men on the US are obese (BMI≤30 kg/m^2). For women in certain ethnic groups, the prevalence is even more striking. Now, the average 20 year-old Black or Hispanic women is obese.

2. Obesity is becoming increasingly prevalent. The overall prevalence of obesity in the US population has tripled since 1975 (1). The incidence of childhood obesity is skyrocketing, and these children are very likely to remain obese in adulthood. But it gets worse. Adults tend to gain even more weight as they age--on the average of 12 pounds per decade in women and 6 pounds per decade in men. Weight gain in adults is most prominent in the decade of the 20's (averaging 17 pounds in this decade) but it continues until average weight peaks in a person's 50's (2).

3. Obesity is a very important health issue. It is estimated that the health costs of obesity exceed 150-200 billion dollars per year in the United States alone. Obesity decreases life expectancy by 2.4 years—more so as the degree of obesity increases. Not only is obesity an important contributor to the prevalence of Type 2 diabetes mellitus and cardiovascular disease, but the number of cancers related to obesity now exceeds cancers caused by cigarette smoking!

In this article, I'm going to discuss the potential causes of obesity. Truth in advertising: the causes are incredibly complex and incompletely understood. In terms of calorie intake, I'll discuss the final common pathway (the hunger and satiety centers in the hypothalamus), but the factors that feed into this pathway--the endocrine system, the GI tract, adipose tissue, neural input from the brainstem all the way to the frontal cortex—are complex and interrelated. Add to this other genetic factors, metabolic energy expenditure, and environmental factors, and the issue becomes incredibly complicated. In the individual patient, there may be many factors that feed into the final common pathway of obesity.

WEIGHT CONTROL AND THE "SET POINT"

It appears that the body has a weight "set point", and that homeostatic mechanisms are employed to defend this weight. For instance, in dietary weight loss, bodily functions change—eating behavior is activated (hunger) and metabolic rate and activity levels decrease--to try to counteract the weight loss. The mechanisms for this homeostatic control are reasonably well understood (see below). But how the body decides on this "set point" is a mystery. And, obviously, for weight to gradually increase throughout the lifetime, factors leading to this "set point" must be imperfectly balanced.

Here's another problem in the study of obesity: minor differences in energy balance (calories in vs. calories out), over long periods of time, can have a major effect on body weight. A calorie excess of just 50 kcal per day (1/2 an apple) will, over a year, lead to the deposition of 5 pounds of fat--over a decade, fifty pounds. Before long, we'd all have our own reality shows on TLC—all due to half an apple a day. Obviously, this doesn't happen to most of people before homeostatic mechanisms kick in. The point, though, is this: small calorie imbalances, over decades, will have major effects.

ENERGY BALANCE: CALORIES IN.

Looking at the problem of obesity simply as an imbalance of calories in vs. calories out oversimplifies the problem. In obesity—especially adult obesity--both issues are probably involved. But it gives us a starting point—a way to organize our discussion of this complex issue. And most recent analyses focus on calories in--continuing excess of calorie intake beyond the homeostatic set point--as the most important factor. So, I will start with calorie intake first.

A. HUNGER AND SATIETY: A COMPLICATED NETWORK CONTROLLING A COMPLEX ACTIVITY

As we have learned more about the genetics of obesity (see the article in this issue by Dr. Contreras), it has become clear that most genetic defects associated with obesity relate to hypothalamic control of hunger and satiety. This is where the various adipose, endocrine, and gastrointestinal factors come together. An imbalance of hormonal signals from each of these systems will converge on the hunger and satiety centers in the hypothalamus. So, let's look at the complex interplay of these various signals.

Adipose tissue factors. The realization that adipose tissue is hormonally active represented a major breakthrough in obesity studies. Before, adipose tissue had been viewed as a passive repository of excess calories; now, a total of 14 "adipokines" (hormonally active substances released by fat cells) have been identified. The most important of these are leptin and adiponectin. Both of these hormones have an anorexigenic (appetite suppress-

ing) effect on the hypothalamus. Leptin was the first discovered, although adiponectin is produced in 5-fold higher quantities and may be equally important. The concept is simple: as obesity develops, the increased fat cell mass causes the leptin level to rise, which then suppresses appetite, returning the organism to baseline weight. Early on, it was thought that a deficiency of leptin might be an important cause of obesity. But it was soon discovered that obese patients actually have higher leptin levels and that exogenous leptin administration is largely ineffective as a treatment for obesity. Now research is focusing on adiponectin and "leptin resistance" as contributing causes of obesity.

Endocrine factors: Insulin has long been known to be involved in energy balance. The rise in blood glucose after a meal directly stimulates insulin release from the pancreas. As the "hormone of anabolism", insulin increases the deposition of calories, including fat calories. Insulin doesn't CAUSE the intake of carbohydrates, but it does help direct the disposal of those excess calories. Furthermore, the insulin resistance that accompanies obesity means that higher levels of insulin are required to do the job. And these relatively high levels are a very important contributor to the complications of obesity. In addition, the pancreatic hormone amylin, which is co-released from beta cells and responds to fat (as well as carbohydrate) intake, has a direct anorexic effect on the hypothalamus and may participate in the feedback loop. Amylin has been developed as a weight-loss agent.

Gastrointestinal factors: The discovery of factors released by the GI tract has been the most exciting and consequential discovery in terms of peripheral factors that modify appetite—especially in terms of treatment. These factors come from the stomach, pancreas, small and large bowel. The most important of these GI factors are the incretins: glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP, also known as glucose-dependent insulinotropic polypeptide). These substances are similar in their insulinotropic effects, but differ in some other respects. GLP-1 is produced by L cells in the lower small bowel and colon, while GIP is produced by more proximal K cells. In addition, GLP-1 responds primarily to carbohydrates in the bowel lumen, while GIP responds to both fats and carbohydrates. Only GLP-1 has vagal effects that decrease gastric emptying. Receptors for both hormones are found throughout the CNS, and both activate the satiety centers in the hypothalamus. Both increase the release of adiponectin from adipose cells, further increasing their appetite-suppressant effects. These beneficial effects, however, may be more important pharmacologically rather than physiologically. Supraphysiologic doses are required to achieve significant appetite suppression, and mutations in receptors that block GLP-1 signaling are not associated with obesity.

Several other GI hormones are involved in appetite control, but I want to emphasize one—ghrelin. Ghrelin is produced by the stomach when it is empty, and is the one GI hormone that stimulates appetite. Ghrelin may be an important contributor to the long-term beneficial effect of weight-loss surgery--in particular, vertical banded gastrectomy—since ghrelin levels decrease by 75% after much of the gastric fundus is removed with this operation.

Where it all comes together: the hypothalamus. Although most of these hormones have systemic effects, their effects on eating behavior come together in the hypothalamus. The fine workings of the hypothalamus have been thoroughly elucidated in recent years, but are too complex for me to discuss here. Suffice it to say that, in response to the anorexic factors mentioned above, activation of certain neurons in the hypothalamus (e.g., by GLP-1) produce satiety, while activation of separate neurons (e.g., by ghrelin) induce hunger. The downstream appetite-suppressing effects are mediated by pro-opiomelanocortin (POMC), melanocyte-stimulating hormones (MSH α and β), and the MSH receptors (especially MC4R). Activation of this satiety pathway leads to suppression of appetite and eating behaviors. Most of the well-characterized genetic mutations that contribute to obesity affect this final common pathway.

The hypothalamus is, of course, affected by all sorts of neural inputs—from the brainstem, the basal ganglia (hence dopamine-stimulated eating behavior), and the higher cortex (conscious and hedonic factors). When all of these factors are integrated together, eating behavior results. And current research suggests that an imbalance favoring calorie intake (i.e., intake above the "set point")—more so than decreased caloric expenditure—is the primary biological driver of the obesity epidemic.

Calorie intake: environmental and "hedonic" factors. These genetic and endocrine factors appear to be important drivers of obesity, but they can hardly be the cause of the rapid increase in the prevalence of obesity in the past few decades. Even considering that epigenetic factors may be passed from obese mother to destined-to-become obese offspring, our genetic code doesn't change that much.

Here, factors like food availability (especially cheap, palatable, high-energy fatty and sugary foods), aggressive marketing tactics, etc. make our subcortical urges easier to satisfy than ever before. That is to say, not all eating behavior is driven by hunger. Stress, social habits ("Let's eat out tonight!") and more conspire with our animal impulses to create a perfect storm for obesity.

B. ENERGY BALANCE: CALORIES OUT

Your energy expenditure consists of 4 factors: resting energy expenditure (formerly called basal metabolic rate), the energy cost of physical activity, the energy required to digest food, and something called adaptive thermogenesis. The latter

2 factors appear to be relatively unimportant. Everybody has to eat, and adaptive thermogenesis—important in hibernating animals and human infants—turns out only to account for 1-2% of total energy expenditure in adults. The dream of activating thermogenic brown or beige fat to burn off our excess calories appears to be unachievable. So, let's look at the first two factors—resting energy expenditure and the energy cost of activity.

Resting energy expenditure (REE)—the energy burned for fundamental cellular processes—accounts for about 60% your total energy expenditure. But, despite that fact that many people ascribe their weight problems to "slow metabolism", this has not turned out to be a major cause of obesity. There IS a lot of inter-individual variation in REE; one study that I found showed the average REE of non-obese people to be 1617 kcal/d, with a SD of 355 kcal—so, again, a large coefficient of variability (3). The catch here is that obese people actually have a greater REE than thin people (in the same study, 1790 kcal/d). So obese patients actually burn MORE energy at rest. This is because, although fat cells themselves have a low metabolic rate, obese people generally have larger internal organs and greater muscle mass. Years ago, there were some tantalizing studies that "pre-obese" children may have a lower REE than their peers, but this has not been borne out by subsequent studies. But differences in RMR may account for some population-wide differences, especially in terms of ethnicity. In particular, Blacks have a slightly lower RMR (1585 kcal/d) than whites (1665 kcal/d in non-obese patients), with a similar difference in obese patients; so RMR may contribute to the well-documented higher rate of obesity in Blacks (especially Black women).

The energy expenditure of activity is extremely variable from one person to another. The major factor here is the energy expended in physical work; stevedores burn much more energy than office workers, for instance. And studies have estimated that, over the past several decades, the energy cost of employment has gone down by about 100 kcal per day (4). On the other hand, it seems likely that energy expended in leisure activities has gone up--although this may be not be true in adolescents, where sedentary activities (e.g., looking at a computer screen) seem to have replaced active play to some degree. In addition (this is something I hadn't thought about), modern heating and air conditioning have decreased the amount of energy we burn in shivering and (to a lesser degree) in sweating.

Finally, I want to mention another source of calorie expenditure which has been hard to quantify—which is, energy burned in purposeless activity (variously called "fidgeting" or "jitter"). A study from years ago, done in a metabolic room where the experimental subjects lived for days at a time, showed that differences in fidgeting could amount to several hundred kcal/day. This conforms to my unpublished observations that non-obese people tend to pace and fidget more than their heavier counterparts. This activity is often ignored in metabolic studies.

Looking at all these data in aggregate, most experts feel that differences in calorie expenditure, although possibly important on an individual level, are less important than calorie intake in accounting for the rising tide of obesity.

AREAS OF CONTROVERSY AND FURTHER STUDY

1. Are **genetics or environmental factors** more important? This is a false dichotomy, since (as in almost all aspects of medicine), both factors play a role. However, current studies in identical twins suggest that 40-70% of obesity is genetic in origin. Over 300 genes have been identified as contributors to obesity—again, more dealing with the brain and hypothalamus than with metabolism and energy partitioning. One way of looking at this is that the genetic factors—most of which have, so far, been related to appetite control--set the stage. Then, envi-

ronmental conditions--i.e., a fast-food restaurant on every corner--make the satisfaction of these drives so much easier.

2. Are **fats or carbohydrates** the main dietary drivers of obesity? This is still an area of controversy. The "fats-are-important-too" group (proponents of the "energy-balance model") focuses on the high calorie density of fats and the failure of high-fat, low carb diets to be more effective than low-fat diets in long-term weight control. Those who emphasize high-glycemic index carbohydrates as the overwhelmingly important culprits (proponents of the "carbohydrate-insulin model") focus on the role of insulin and insulin resistance. An interesting point-counterpoint debate detailing these viewpoints can be found in a recent publication (5,6).

3. What role does the **human microbiome** play in obesity? This perspective came to the fore when a few patients with obesity seemed to improve after fecal microbiota transplant (FMT) done for other reasons. Indeed, comparison of the fecal microbiome in normal-weight vs obese patients has shown substantial differences: the microbiome in obese patients is less diverse and is relatively poor in certain species (e.g. Lactobacilli and Bifidobacterium). And gut bacteria can affect appetite (via hormone-like byproducts) and can even increase available calories (by breaking indigestible fiber down into absorbable small molecules like short-chain fatty acids). However, supplementing obese patients with probiotics hasn't been helpful, and I came across one meta-analysis of 10 controlled trials (N=334 patients) that found no significant difference between obese patients who received FMT and a control group (7).

4. Why is **dietary weight loss so slow and so difficult to sustain** (except after bariatric surgery)? Only about 20% of patients are able to keep their weight off with dietary means alone. We have discussed the fact that weight loss leads to metabolic changes (in resting metabolic rate, in thyroid hormone metabolism, in muscle energy efficiency, in leptin and adiponectin) that try to minimize the amount of weight lost. There is increasing evidence that these changes persist even if weight increases back to baseline—making further attempts at weight loss by dietary means ever more difficult (8).

5. What are the causes of the **cardiovascular and carcinogenic consequences of obesity?** Although anatomical effects of obesity (osteoarthritis, GERD, sleep apnea) are important, the major causes of increased mortality in obese patients are cardiovascular disease and cancer. But there are no adipocytes in atherosclerotic plaques, and liposarcomas are extremely rare in obese (as in non-obese) patients. So, what are the mechanisms of this downstream effect? The major contributors appear to be insulin resistance and the low-level chronic inflammation that accompany obesity. Abdominal obesity, in particular, is a particularly potent cause of insulin resistance. In addition, ectopic fat (e.g., fat in the liver) makes a separate contribution to insulin resistance. Finally, adipose tissue in obese patients has an increased rate of apoptosis and is infiltrated with large numbers of macrophages, factors that contribute to inflammation. This is an area of active study.

CONCLUSIONS

Our understanding of the causes of obesity has moved far beyond the accusations of failure of will power and fat-shaming of decades ago. Our current synthesis focuses on the failure of the homeostatic "set-point" by a combination of genetic factors (mostly relating to imbalances in hunger/satiety centers in the hypothalamus), combined with environmental factors (less physical activity, easier access to cheap, palatable, high caloric-density foods). Genetic factors play a major role in childhood obesity and the weight gain that occurs around puberty and early adolescence, while environmental factors may play a greater role in the gradual weight gain of adulthood. Fortunately, advances in scientific understanding of the factors involved--combined with serendipity (GLP-1s, developed to treat diabetes, were found to have important anorexic effects) plus effective surgical options--have come together to provide useful options for the modern management of obesity.

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The Genetics of Obesity:
Understanding the Role of Key Genes

by Maria F Contreras, MD
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INTRODUCTION

Obesity is a complex disease that is influenced by genetics, environment, and their interactions. As the prevalence of obesity worldwide continues to rise, untangling its causes has the potential to explain its pathophysiology and therapeutic targets with the broader goal of reducing the health burden on people. Twin studies have estimated the heritability of body mass index (BMI) to be between 40 and 77% (1). Family and adoption studies show a stronger correlation between adoptees and their biological parents than with their adoptive parents.

Genetic and syndromic forms of obesity account for an important but frequently underdiagnosed portion of severe obesity cases. Genetic and epigenetic factors play a vital role in the pathogenesis of obesity. Obesity affects over 650 million adults worldwide, with most attributed to polygenic factors combined with environmental influences. While monogenic and syndromic forms of obesity are rare, recognizing them is essential, as accurate diagnosis directly informs targeted treatment strategies and optimizes patient outcomes. These genetic forms of obesity typically present with severe, early-onset obesity accompanied by distinctive clinical features that differentiate them from typical polygenic obesity (2).

Research in obesity has progressed rapidly; however, the rise in obesity rates continues to outpace these advances. Over the last 30 years, evidence has shown that weight gain is driven largely by complex biopsychosocial influences rather than individual willpower alone. Numerous genetic variants have also been identified that increase susceptibility to obesity, particularly when interacting with today's obesogenic environment. Obesity of genetic origin is classified into a polygenic and a monogenic form, although recent findings indicate a significant overlap between these two groups (3).

OBESITY- RELATED GENES

Monogenic obesity results from a mutation or deficiency of a single gene and is a rare but severe cause of obesity. It occurs when there is a mutation in one of the genes involved in the leptin–melanocortin pathway.

New advances in genetic evaluation and analysis have led to the identification of obesity-related genes. For example, eight genes have been reported as loci for obesogenic mutations, including mutations in genes affecting the structure of leptin (LEP), the leptin receptor (LEPR), proopiomelanocortin (POMC), prohormone convertase 1 (PCSK1), the melanocortin 4 receptor (MC4R), single-minded homolog 1 (SIM1), brain-derived neurotrophic factor (BDNF), and the neurotrophic tyrosine kinase receptor type 2 gene (NTRK2) (4).

LEPTIN:

Leptin is a protein secreted by white adipose tissue; it binds to the leptin receptor (LEPR) which is ubiquitously expressed, particularly in hypothalamic neurons. The activation of LEPR elicits the critical role of leptin in energy balance and body weight homeostasis. In physiologic conditions, increased white adipose cell mass causes a rise in serum leptin levels, which in turn reduces appetite. Specifically, when leptin binds to LEPR in the hypothalamus, it generates α-melanocyte-stimulating hormone, which then activates the melanocortin-4 receptor (MC4R), inducing satiety (5). Mutations in LEP cause a monogenic form of obesity characterized by hyperphagia and rapid weight gain starting in the first months of life. Its prevalence is estimated to be 3% of childhood-onset obesity (6), although the mean age at genetic diagnosis is 18 years old.

LEPR mutations cause a leptin-resistant state with permanent hyperphagia leading to severe obesity. LEPR mutations are associated with hyperphagia, which leads to severe obesity evidenced before 5 years old or earlier (e.g., during

the first months of life). Additionally, another important clinical finding associated with LEPR mutations is hypogonadotropic hypogonadism (7). It is currently admitted that adequate leptin signaling is necessary for the onset of puberty and for pubertal growth (8). The pulsatile secretion of GnRH, which triggers LH and FSH secretion and gonadal activation, is altered in these patients, as leptin is a crucial modulator of a suitable pulsatility of GnRH that activates the hypothalamic–pituitary–gonadal axis. The anorexigenic effect of leptin is also functionally disrupted in patients with sporadic obesity, indicating that leptin resistance is common in these individuals. Indeed, serum leptin levels were found to correlate positively with the amount of body fat in non-genetic obesity (8).

PROOPIOMELANOCORTIN (POMC) DEFICIENCY

Pro-opiomelanocortin (POMC) is a critical precursor protein in the melanocortin pathway that regulates appetite and energy balance, and mutations or deficiencies in POMC cause severe early-onset obesity due to hyperphagia (8). POMC is processed into melanocyte-stimulating hormones (α-MSH and β-MSH) that activate melanocortin-4 receptors (MC4R) in the hypothalamus to suppress appetite and increase energy expenditure (8).

Genetic POMC deficiency results in one of the most severe forms of monogenic obesity. Patients with biallelic POMC mutations present with early-onset severe obesity, hyperphagia, hypopigmentation (pale skin and red hair due to lack of melanocortin-1 receptor activation), and adrenocorticotropic hormone (ACTH) deficiency leading to hypocortisolism (9). These individuals lack the melanocortin peptides necessary for satiety signaling, resulting in uncontrolled hunger starting in infancy (9).

MELANOCORTIN-4 RECEPTOR

The melanocortin-4 receptor (*MC4R*) gene is now considered the most common associated gene for childhood obesity; it was found in about 4% of affected cases prior to advanced genetic testing and next generation sequencing (10). It was first discovered to be related to body weight in 1998, and now multiple studies have investigated its mechanism and the function of different mutations (11). The *MC4R* gene codes for the *MC4R* protein, which plays an important role in energy homeostasis and food intake behavior (12). The central melanocortin pathway regulates energy balance and homeostasis by activating or inhibiting leptin; its receptor is mediated by two subsets of neurons as well as *MC3R* and *MC4R* in the arcuate nucleus of the hypothalamus.

PCSK1 (PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 1)

PCSK1 mutations cause monogenic obesity through impaired processing of POMC and other prohormones in the leptin-melanocortin pathway. Biallelic PCSK1 deficiency results in severe early-onset obesity with hyperphagia, similar

to POMC deficiency, along with malabsorptive diarrhea, hypoadrenalism, and abnormal glucose homeostasis (4). The enzyme PCSK 1/3 is essential for converting proinsulin to insulin and proglucagon to active forms, explaining the metabolic abnormalities beyond obesity.

CHROMOSOMAL DEFECTS AND OBESITY

Syndromic childhood obesity is a rare form of obesity that is part of multiple clinical manifestations. Advanced genetic testing has helped in the detection of defects at the chromosomal and DNA levels and has improved the diagnosis of both rare and common forms of obesity. The determination of genetic causes of obesity is helpful for genetic counselling and the selection of appropriate treatment. In addition, Dasouki et al. and Cheon et al. have each summarized chromosomal abnormalities with syndromic obesity (13,14). Kaur et al. reported 79 obesity syndromes described in the literature, with obesity considered to be a cardinal feature in 55 of them, while the prevalence of obesity in the other 24 syndromes was higher than in the general population. Forty-nine syndromes have been mapped to specific chromosome regions or locations, including a causative gene (15). Some examples of syndromic obesity due to chromosomal defects more commonly seen include Prader–Willi syndrome (PWS), Down syndrome, Bardet–Biedl syndrome, fragile X syndrome, Alstrom syndrome, and Cornelia de Lange syndrome.

CONCLUSION

Genetics play a critical role in the development of obesity, particularly in children with early-onset or severe disease. Variants in genes such as *POMC, PCSK1, LEPR,* and *MC4R* highlight the importance of the hypothalamic pathways that regulate appetite, satiety, and energy balance. In addition, genetic and syndromic forms of obesity demonstrate that excess weight is not simply the result of lifestyle choices, but often reflects underlying biologic drivers.

Recognizing genetic contributors is essential for clinical practice. Identification of monogenic obesity—characterized by severe early-onset obesity (before age 5), hyperphagia, and often a positive family history—enables access to targeted therapies. Setmelanotide, a melanocortin 4 receptor agonist, is FDA-approved for patients with POMC, PCSK1, or LEPR deficiency, as well as Bardet-Biedl syndrome.

Genetic testing is recommended for patients presenting with rapid weight gain in infancy, severe obesity, hyperphagia, and additional clinical features such as endocrine abnormalities. Early identification improves diagnostic accuracy, reduces stigma, guides personalized treatment approaches, and prevents the development of obesity-related complications.

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Obesity as a Chronic Disease: Health Benefits Beyond Weight Loss

by J. Drew Payne, DO FACP DABOM

Many people struggle with weight issues. The cycle of gaining, dieting, losing, and gaining again brings stress to the body and the emotions. The latest medical research provides powerful motivation to increase overall health by addressing weight issues. Losing the extra pounds will lower blood pressure, reduce cardiovascular events, improve metabolic disease, and alleviate mechanical and inflammatory complications across multiple organ systems.

For decades, obesity was viewed primarily as a consequence of individual behavior. Medical students were taught that too many calories and too little exercise led to excess weight. This simplistic framing failed to account for the complexities truly driving this issue. As a result, obesity was often treated as a cosmetic concern and sometimes as the fault of the patient, one of the seven deadly sins. That perspective changed formally in 2010 when the World Health Organization classified obesity as a chronic disease (1). This designation reflected mounting evidence that excess adiposity produces predictable pathophysiologic changes and increases morbidity and mortality. Obesity shares core defining characteristics of a chronic disease: it follows a relapsing course, it involves dysregulated physiology rather than moral failure, and it benefits from long-term management rather than episodic advice.

Obesity is commonly defined using the body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. A BMI of 30 kg/m² or higher meets the clinical definition of obesity. While BMI is an imperfect surrogate for body fat distribution and metabolic health, it remains a practical population-level screening tool that correlates with disease risk across diverse populations.

The recognition of obesity as a disease has led to a reframing of treatment goals. Weight loss itself has become less important than its downstream effects on blood pressure, glucose regulation, cardiovascular risk, joint health, and quality of life. Over the last 15 years, particularly with the expansion of bariatric surgery and explosion in popularity of glucagon-like peptide-1 (GLP-1) receptor agonists, research has clarified that intentional weight loss produces meaningful benefits across multiple organ systems.

HYPERTENSION

Hypertension represents one of the most direct and consistently reversible consequences of obesity. Excess adipose tissue drives blood pressure elevation through several mechanisms: activation of the sympathetic nervous system, stimulation of the renin-angiotensin-aldosterone system, sodium retention, endothelial dysfunction, and structural changes in the kidney (2). Visceral fat, in particular, accounts for 65% to 75% of the risk for primary hypertension (2). Conversely, weight loss reliably lowers blood pressure, often reducing or eliminating the need for antihypertensive medications. Clinical trials suggest that a 5-10% reduction in body weight can lower systolic blood pressure by 5-10 mm Hg, an effect comparable to first-line pharmacologic therapy.

More substantial weight loss yields even greater benefits. Bariatric surgery studies show remission of hypertension in a significant proportion of patients, particularly when intervention occurs earlier in the disease course (3). Similarly, trials of GLP-1 receptor agonists and dual incretin agents demonstrate consistent reductions in blood pressure independent of weight loss alone, suggesting favorable effects on vascular function and sodium handling. Taking this one step further, lower blood pressure translates into fewer strokes, less heart failure, and reduced progression of chronic kidney disease. Finally, for patients struggling with polypharmacy, weight-centered treatment allows for patients to reduce the number of medications they take overall.

OTHER CARDIOVASCULAR CONDITIONS

The relationship between obesity and cardiovascular disease is also now well documented. Obesity accelerates atherosclerosis through insulin resistance, dyslipidemia, systemic inflammation, and endothelial dysfunction. It increases the risk of coronary artery disease, heart failure, atrial fibrillation, and sudden cardiac death. Long-term observational data from bariatric surgery cohorts demonstrate substantial reductions in myocardial infarction, stroke, and cardiovascular mortality. Patients undergoing metabolic surgery experience sustained improvements in lipid profiles, inflammatory markers, and cardiac structure (3). Pharmacologic therapies have added further clarity. Recent randomized trials of GLP-1 receptor agonists in patients with obesity have shown reductions in major adverse cardiovascular events (4). These benefits appear to extend beyond blood sugar improvement, as they are present in patients without diabetes.

Obesity drives the development of heart failure with preserved ejection fraction (HFpEF), which now accounts for nearly half of all heart failure cases.

Weight loss lowers left ventricular filling pressures. Patients with HFpEF report improvement in exercise capacity and reduction of symptoms after weight loss. In a condition with few effective treatments, addressing obesity offers one of the only ways to meaningfully change the course of HFpEF.

Taken together, these findings support a major shift in medicine. Weight loss is no longer viewed merely as risk factor modification but as active cardiovascular therapy. Treating obesity alters the trajectory of heart disease in addition to preventing it.

METABOLIC CONSEQUENCES OF OBESITY: TYPE 2 DIABETES AND MAFLD

Amazingly, metabolic consequences of obesity extend well beyond hypertension and heart disease. Excess adiposity disrupts insulin signaling, leading to insulin resistance and type 2 diabetes mellitus. Even modest reductions in body weight enhance insulin sensitivity and lower fasting glucose levels. Significant and sustained weight loss can induce diabetes remission, particularly when achieved early in the disease course. Bariatric surgery studies report long-term remission rates that far exceed those seen with medication alone (5).

Metabolic associated fatty liver disease (MAFLD), now the most common cause of chronic liver disease in the United States, also responds dramatically to weight reduction (see article by Dr. Lusby in this issue). Weight loss removes pro-inflammatory fat in the liver. In time, the reduction in fat decreases the fibrosis and scarring which drive chronic liver disease. MAFLD, similar to HFpEF, responds weakly to approved therapies; so weight loss becomes the main avenue to treat and not simply prevent MAFLD.

The list truly goes on and on. Obesity worsens osteoarthritis, obstructive sleep apnea, gastroesophageal reflux disease, and polycystic ovary syndrome. In each case, weight loss improves symptoms and disease severity, often reducing the need for long-term pharmacologic therapy. These improvements translate into better mobility, better sleep quality, better fertility outcomes, and overall better quality of life.

The growing body of evidence is clear: treating obesity improves health in ways that extend far beyond appearance or cosmetic outcomes. Weight loss lowers blood pressure, reduces cardiovascular events, improves metabolic disease, and alleviates mechanical and inflammatory complications across multiple organ systems. And, more importantly, the paradigm has continued to shift to knowledge that these benefits arise not from willpower alone but from targeted medical and surgical therapies that address the underlying biology of obesity.

As clinicians, recognizing obesity as a chronic disease obligates us to treat it with the same seriousness as the diseases it causes. As new therapies expand our ability to do so, the focus should remain on what matters most: treating the patient as a whole, through prevention of disease and optimizing health.

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Primary Care Perspective on Obesity in the Texas Panhandle

by Montana O'Dell, MD and Marlene Jantes

INTRODUCTION

The American Academy of Family Physicians describes obesity as a chronic, multifactorial condition with genetic, epigenetic, metabolic, hormonal, cultural, socioeconomic, and neurobehavioral causes. This description can seem overwhelming in both its causes and treatments, and even more daunting for a primary care physician practicing in Amarillo, where in 2020 the prevalence of obesity was 49.2% among adults (5). As a primary care physician, where does one begin in addressing the causes and treatment of such a complex disease? Amid the challenges of medicine, it is important to remember that, as physicians, we are scientists. The core principle of science is to identify a problem or behavior and ask, "Why?" In this case, the question becomes: why does a city that is predominantly conservative, religious, rural, working-class, and proud of its Texas heritage have such a high prevalence of obesity? The answer lies in understanding the selective pressures that drive a population toward disease.

During my undergraduate studies at Texas Tech University, I majored in biology and conducted research on American hog-nosed skunks (Conepatus leuconotus) with a PhD candidate, Adam Furgeson. We studied the body habitus and stripe patterns of this species across a range from Colorado to Mexico. Our research was based on an ecological principle called Bergmann's Rule, which states that organisms in colder environments are larger than those in warmer environments due to surface-to-volume ratios. We examined environmental pressures, such as temperature and resource availability, that influenced the skunk phenotype. This concept of environmental pressures shaping phenotype reappeared during my medical studies at Texas Tech Paul L. Foster School of Medicine in El Paso. I was assigned to a public school system where I screened Mexican children along the border for a condition called acanthosis nigricans. This condition appears on flexion points of the skin where high cellular turnover is stimulated by the growth factor, insulin. Children with this skin manifestation were highly likely to develop diabetes and obesity in adulthood. The environmental pressure driving this condition was hyperinsulinemia due to easy access to refined carbohydrates and processed foods.

During this period, I also published a meta-analysis with bariatric surgeon, Dr. Benjamin Clapp, entitled "Long-Term (7 or More Years) Outcomes of Sleeve Gastrectomy: A Meta-Analysis" (1). We found that 27.8% of patients who had more than 75% of their stomach removed nonetheless failed to maintain weight loss after seven years. Why do 27.8% of patients fail despite optimal surgery? Even with the best surgical technique addressing all metabolic, hormonal, and neurobehavioral factors, cultural and socioeconomic influences remain major forces that are difficult to control. This illustrates why obesity as a chronic disease is multifactorial and requires a comprehensive strategy and a dedicated care team.

DEALING WITH THE "FAST-FOOD CULTURE"

Why do such a large percentage of adults in Amarillo suffer from obesity? In my clinic, which serves patients from low-income to upper-middle-class backgrounds, cultural and socioeconomic factors strongly drive overconsumption of refined carbohydrates and processed foods. Amarillo and its surrounding areas have a culture of fast food, oversized portions, sweet tea, sodas and other sugary drinks (often with free refills), high-carb Mexican food, and numerous convenience stores that sell mostly processed foods. All of these factors, combined with limited access to grocery stores offering healthy foods in rural areas, leads to the issue of overconsumption of these addictive refined carbohydrates. For many, this overconsumption is a maladaptive coping mechanism, an unhealthy and ineffective way to manage stress, adversity, or emotional distress. In my opinion, this represents the major driving force for obesity in the Texas Panhandle. The population has been conditioned by an environment designed to reinforce these negative behaviors, often for monetary gain.

If physicians have no control over the food industry and its lobbying, what then controls our patients' healthcare environment in addressing obesity? In this regard, major influences are insurance companies and professional medical organizations, which shape healthcare pressures through coverage policies and guidelines. In my clinic, fewer than 10% of patients work for companies that provide insurance coverage for GLP-1 medications for obesity. Insurance will cover the evaluation and treatment of complications caused by obesity--such as metabolic-associated fatty liver disease (MAFLD), obstructive sleep apnea (OSA), hypertension, diabetes, joint replacement, and hormonal imbalances--but not the underlying disease itself. This reality led me to venture outside standard clinical norms and begin prescribing compounded GLP-1 medications to ensure access for my community.

BEHAVIORAL AND NUTRITIONAL ASSESSMENT

One of my favorite quotes in my weight-loss clinic is from Hippocrates: "Before you heal someone, ask him if he is willing to give up the thing that makes him sick." (2). In obesity, that "thing" is often the overconsumption of processed foods and sugar, which can be addictive. During my assessment of patients with obesity, I begin with a behavioral evaluation, asking about coping mechanisms, daily routines, and sleep patterns. Sleep hygiene is one of the most important concepts I teach, as many patients with obesity struggle to initiate or maintain sleep. They may develop maladaptive behaviors, such as using food to cope with insomnia. I spend time counseling patients on strategies to initiate and maintain healthy sleep, which include limiting screen time, avoiding social media and news before bed, setting boundaries, and minimizing conflict.

I then evaluate the patient's environment, including work stressors, family dynamics, socioeconomic conditions, and cultural practices. Nutritional counseling follows, where we discuss what patients eat, where they purchase food, and their eating behaviors and patterns. I help patients understand why their current eating patterns contribute to obesity and emphasize sustainable strategies, such as a diet of unprocessed foods combined with intermittent fasting-- typically a 16-hour fast—and carbohydrate intake of less than 100 grams daily. Depending on individual circumstances, we develop a strategy to integrate these habits sustainably into daily life.

Accountability is a critical component of success. I schedule weight-loss visits every 6–8 weeks with modest goals of losing 1–2 pounds per week. Patients need ongoing education, redirection, and support to establish and maintain new behaviors. I provide recommendations for practical tools, such as the Ninja Foodi Grill XL, to teach meal preparation and encourage healthy eating. I also coordinate support from nutritionists, counselors, pastors, gym trainers, and senior citizen clubs to reinforce lessons learned in the clinic. Building new coping mechanisms is challenging, but, with the right support, it can be accomplished.

MEDICATIONS AND LONG-TERM MANAGEMENT

Medication options are limited by insurance coverage, complex prior authorization processes, contraindications, cost, patient occupation (e.g., pilots and truckers cannot use stimulants), and pharmacy availability (3). GLP-1 receptor agonists are the primary medications I prescribe for weight loss, starting with semaglutide before tirzepatide. I choose this approach because semaglutide is more readily available, is covered by more insurance plans, and is cost-effective on the compounding market. Tirzepatide offers superior sati-

ety and a better GI side-effect profile due to the GIP component. I find that tirzepatide works best for certain patients, especially women in peri- or post-menopause and those with IBS or IBD. I rarely use oral semaglutide because of minimal bioavailability due to poor gut absorption. Injectable peptides offer better bioavailability and are preferred for higher efficacy and adherence in comparison to a daily pill.

Patients often plateau after losing about 40 pounds while on GLP-1 therapy, especially on high dosages. In such cases, I occasionally implement a "washout" period (based on clinical experience, not formal studies), using phentermine, a medication approved for short term management of obesity, or Vyvanse, a medication indicated by the FDA for binge eating disorder, for four to six weeks, pausing the GLP-1, then resuming and titrating the GLP-1 dose with continued intense counseling. Some patients, particularly younger women needing to lose 20 pounds, may succeed with phentermine alone.

The Obesity Medicine Association has released a statement against compounded GLP-1s, noting: "Obesity is a serious disease; FDA-approved treatment that is effective and safe is available. Please use the same care when treating obesity as you would any other serious medical condition." (4). While this statement is accurate from a regulatory perspective, it fails to account for patients who cannot access FDA-approved therapies due to systemic barriers. For the past four years, I have worked with a trusted compounding pharmacy and have observed remarkable results in my patients and community. Healthcare organizations are often out of touch with the realities of our patient's lives. As providers, it is our responsibility to ensure that our patients have access to safe, effective, and practical treatments. Obesity must be treated as a chronic disease, with the same intensity and multidisciplinary approach as other chronic conditions.

Obesity is not simply the result of individual choices. It is the product of genetic predisposition, cultural conditioning, environmental pressures, and socioeconomic realities. In Amarillo, these pressures create a culture of overconsumption of processed foods and unhealthy behaviors. Yet, through behavioral assessment, environmental evaluation, nutritional counseling, sleep management, social support, and pharmacologic therapy when indicated, primary care physicians can make a meaningful impact. Treating obesity requires persistence, education, creativity, and empathy. Most importantly, it requires acknowledging that patients live within environments that shape their behaviors and health and then addressing not only the biological but also the behavioral, cultural, and environmental factors that drive this chronic disease.

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New Tools for Weight Loss:
Understanding Incretins and What's Coming Next

by Brian Terrell, Pharm.D., BCACP

The appetite for incretin therapeutics has increased dramatically in recent years, despite the exact opposite physiologic effect in patients (1). What started as a breakthrough in type 2 diabetes has evolved into a tremendous shift in the metabolic management of obesity and its resulting comorbidities. Results from clinical trials and real-world experience back up the efficacy of these agents and are a driving force behind their popularity. The rapid increase in demand for these agents also creates some interesting questions and challenges. This brief review will address what's now, new, next, and notable in incretin therapy for weight loss in patients without diabetes.

WHAT'S NOW?

Targeting glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors with hormone agonists has multiple effects on the body. GLP-1 agonists reduce appetite, delay gastric emptying, modulate reward pathways to decrease cravings, and increase insulin secretion through binding to receptors in many different organ systems, including the central nervous system (CNS), intestines, and pancreas (1). GIP adds enhanced energy balance regulation within the CNS and in adipose tissue (2). There are four formulations (three molecules) approved, with three having more extensive data for use.

The first injectable incretin approved for weight loss was Saxenda® (liraglutide), followed by its fellow injectable GLP-1 agonist Wegovy® (semaglutide), and finally by the dual GIP/GLP-1 agonist Zepbound® (tirzepatide). Clinical trial data show significant weight loss with all agents at maximum doses with varying magnitudes. All clinical trials were conducted with lifestyle intervention coaching as a baseline for participants in both treatment and placebo groups. Mean total weight loss amounts from clinical trials are listed in Table 1, while comparative results to placebo and any additional benefits identified are discussed in the text below.

Liraglutide at a dose of 3 mg once daily compared to placebo significantly reduced weight by 4.3-5.4% in patients without diabetes over 1-3 years. Significantly more patients than controls lost >5% or >10% of their body weight, and treated patients had a reduced risk of developing diabetes (3-5).

Semaglutide at a dose of 2.4 mg once weekly significantly reduced weight by 10.4-12.6% compared to placebo over 1-2 years. In this study as well, more patients than controls lost >5%, >10%, and >15% of their body weight (6-8). Injectable semaglutide also demonstrated a reduced risk of composite cardiovascular events compared to placebo in patients without diabetes (HR 0.80, 95% CI 0.72-0.90) and improvement in metabolic dysfunction–associated steatohepatitis (MASH) and heart failure with preserved ejection fraction (HFpEF) (9-11).

Tirzepatide across doses of 5 mg, 10 mg, and 15 mg demonstrated mean weight loss ranging from 11% to over 20% compared to placebo, with more than half of patients at the highest dose losing ≥20% of their body weight (12, 14). In a comparison to maximally tolerated dose of injectable semaglutide, tirzepatide reduced body weight a further 6.5% (13). Tirzepatide has also demonstrated improvements in outcomes in patients with obstructive sleep apnea, heart failure with preserved ejection fraction, and metabolic dysfunction-associated steatohepatitis (MASH) (15-17).

It is not all good news, as there are some significant concerns regarding appropriate use, and side effects can be intolerable for some. The indications for liraglutide and injectable semaglutide for weight management are as adjuncts to diet and exercise in adults and pediatric patients at least 12 years old (weighing at least 60 kg) with obesity or in adults with overweight and at least one weight-related comorbid condition (18-19). Tirzepatide is only approved in adults (20). All of the agents are contraindicated in people with a personal or family history of medullary thyroid tumors or in patients with multiple endocrine neoplasia type 2 (MEN2). They also carry precautions about use around surgical procedures (18-20). The most common adverse effects of these agents are gastrointestinal in nature, including abdominal pain, constipation, diarrhea, nausea, and vomiting, but there are also concerns about acute kidney injury, gallbladder disease, and pancreatitis (18-20). The FDA recently removed the warning about suicidal ideation or behavior after a comprehensive review (21). Recent reporting emphasizes that not all patients will see the dramatic weight loss results seen in clinical trials, owing to different drivers and phenotypes of obesity--thus highlighting the importance of an individualized approached to obesity management (22).

WHAT'S NEW?

The newest approved agent is the tablet form of Wegovy® (semaglutide), which received approval in December 2025 (23). At a dose of 24 mg once daily, oral semaglutide significantly reduced weight by 11.4% compared to placebo over 64 weeks, and 29.7% of patients were able

to lose at least 20% of their body weight with a similar side effect profile as the injectable form (24). Like its counterpart approved for diabetes (Rybelsus®), the peptide nature of the drug requires specific administration steps (in the morning on an empty stomach with up to 4 ounces of plain water only, at least 30 minutes prior to food, other beverages or medications) for adequate oral absorption, leading to potential issues with compliance and timing/spacing of other medications (19).

WHAT'S NEXT?

Orforglipron, an oral, small molecule, non-peptide GLP-1 agonist is being investigated for weight loss. Recent clinical trials demonstrate significant weight loss, with the highest dose (36 mg once daily) reducing weight by 9.1% compared to placebo; 18.4% of patients in this group lost at least 20% of their body weight with a similar side effect profile to other GLP-1 agonists (25). This formulation removes the concerns about administration that plague oral Wegovy® and Rybelsus® (described above) and will potentially increase access to weight loss medications for more people.

Retatrutide includes glucagon agonism to add a triple "G" agonist to the once-weekly injectable incretin line up and is being investigated for weight loss and other benefits. Along with GLP-1 and GIP (the main targets), the addition of glucagon is purported to further reduce energy intake and/or increase energy expenditure (26). The most recent trial results are impressive, demonstrating the highest magnitude weight loss of any of these group of agents. Preliminary results from the phase 3 TRIUMPH 4 trial demonstrated that retatrutide at a dose of 12 mg once weekly reduced weight by 26.6% compared to placebo at 68 weeks; 58.7% of patients lost at least 25% of their body weight and 23.7% of participants lost at least 35% of their body weight with similar side effects as other incretin agents, with the exception of higher rates of dysesthesia events (27). This study also demonstrated improvements in symptoms of osteoarthritis the knee (27).

Cagrilintide-semaglutide is also being investigated for weight loss. Cagrilintide adds amylin agonism, which is purported to help further regulate energy intake (28). In the phase 3a REDEFINE-1 trial, the once-weekly combination of cagrilintide 2.4 mg and semaglutide 2.4 mg reduced weight 17.3% compared to placebo at 68 weeks; 53.6% of patients lost at least 20% of their body weight and 19.3% of patients lost at least 30% of their body weight with a similar side effect profile as other incretin agents (28).

WHAT'S NOTABLE?

Dosing strategies for these agents follow titration schedules for tolerability, so it is important to understand that patients may not see much effectiveness

Table 1: Comparison of Incretin Agents in Patients without Diabetes for Weight Loss

Agent	Mechanism	Route	Typical Max Dose	Mean Weight Change at Highest Dose from Weight Loss Trials
Currently Available Agents				
Saxenda® (liraglutide)	GLP-1 Agonist	Subcut	3 mg daily	-6.5-8.4 kg (over 1-3 years)
Wegovy® (semaglutide)	GLP-1 Agonist	Subcut	2.4 mg weekly	-15.3-16.8 kg (over 1-2 years)
Wegovy® (semaglutide)	GLP-1 Agonist	Oral	25 mg daily	-14.2 kg (over 64 weeks)
Zepbound® (tirzepatide)	GIP/GLP-1 Agonist	Subcut	15 mg weekly	-21.4-23.6 kg (over 72-176 weeks)
Investigative Agents				
Orforglipron	GLP-1 Agonist	Oral	36 mg daily	-12.4 kg (over 72 weeks)
Retatrutide	GIP/GLP-1 /GCG Agonist	Subcut	12 mg weekly	-32.3 kg (over 68 weeks)
Cagrilintide / Semaglutide	Amylin / GLP-1 Agonist	Subcut	2.4 mg/2.4 mg weekly	-21.6 kg (over 68 weeks)

Abbreviations: GLP – glucagon like peptide; GIP - glucose-dependent insulinotropic polypeptide; GCG – glucagon; Subcut - subcutaneous
Information from references 3-8, 12, 14, 18-20,25, 27 and 28.

at the first or even second dosage levels (18-20). Duration of treatment is also a topic of intense interest, as recent investigations demonstrate the regain of significant amounts of weight after discontinuation of the medications (29). The optimal strategy has not been identified, but incorporation of healthy habits during weight loss (such as resistance training to prevent lean muscle loss, attention to adequate protein intake, and portion control) are essential for both healthy weight loss and to minimize weight regain upon discontinuation (29).

The popularity of these agents has led to issues with access, but shortages have been reported to be resolved at the time of this publication. During the time of shortage, compounded products gained popularity but are now facing regulatory and quality issues; efforts should be made to ensure that patients are receiving approved and standardized medications (30-31). The most recent trend of concern involves individuals obtaining research grade retatrutide through unofficial sources, putting them at risk of poor outcomes (32).

Insurance coverage and costs can be significant barriers to the use of these medications, even with savings cards from manufacturers, especially for long term use (33).

Since these medications slow gastric emptying, there is a concern about slow absorption of oral medications, with particular attention pointed at oral contraceptives. Tirzepatide prescribing information instructs women taking this medication to switch to a non-oral contraceptive or to use a barrier method for at least 4 weeks at time of initiation and around any dose change of the weight loss medication (20).

CONCLUSION

Incretin therapies have changed the landscape of obesity management, and new agents appear poised to continue that trend. Ongoing and future investigations will continue to elucidate potential additional benefits of these medications. Appropriate use and informed, shared decision making with patients will be paramount to long-term success of weight loss with this group of medications.

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Surgical Considerations for Management of Obesity

by LaJohn Quigley, MD, FACS

Obesity is a chronic medical condition that affects many individuals and has reached pandemic levels worldwide. The current prevalence of obesity in the United States is approximately 40.3%, with 9.4% of patients suffering from severe obesity. Excess body fat increases the risk for health conditions such as diabetes, hypertension, stroke, heart disease, and certain types of cancer. Management of obesity and obesity-related conditions continues to be a challenging topic for patients and physicians alike. With newer medications available to help with weight management (i.e., GLP-1 agonists), there has been a decline in patients seeking and undergoing weight loss surgery. Unfortunately, even prior to the surge of GLP-1 medications, only about 1-2% of eligible patients undergo surgery.

Bariatric (weight loss) surgery is a proven medical option for people with obesity who have not achieved lasting results with diet, exercise, and medication. Beyond helping patients lose weight, these procedures can significantly improve or even resolve obesity-related conditions such as type 2 diabetes, high blood pressure, and sleep apnea and can improve quality of life. Bariatric surgery has shown excellent results in terms of controlling obesity-related conditions and remains comparatively safe. With an ever-increasing number of patients living with obesity, the need for bariatric surgery is likely to increase. This article explains the most common surgical techniques, how they work, expected outcomes, benefits, and potential risks

INDICATIONS FOR SURGERY

The indications and qualifications for bariatric surgery differ across insurance providers. In 1991, the American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) released a consensus statement advocating " bariatric surgery confined to patients with a BMI of at least 40 or a BMI of 35 or more and at least one obesity-related condition such as hypertension or heart disease". This statement was updated in 2022, stating that they "recommend metabolic and bariatric surgery for individuals with a BMI of 35 or more regardless of presence, absence, or severity of obesity-related conditions" and that it be considered for people with a BMI of 30-34.9 and metabolic disease, as well as for "appropriately selected children and adolescents". Although this update was released several years ago, insurance providers have been slow to adapt to the new recommendations. Many insurance providers adhere to the prior statement that patients require a BMI of 35 or greater and a least one obesity-related condition. Few providers will cover surgery for patients with BMI of 40 or greater without an obesity-related condition. Medicaid is one of the few providers that offer surgery for their patients who meet the new criteria. Even more frustrating to patients, not all plans are the same. Having commercial insurance doesn't guarantee that your surgery will be covered. Each individual's plan will determine whether they qualify for bariatric surgery or not. Cash pay options allow the indications for surgery to be broader and surgeon-specific. Generally, for insured patients with coverage for bariatric surgery, the indications for surgery are:

- Adult patients with BMI of 35 or more with an obesity-related comorbidity
- Pediatric patients age 13-18 with BMI of 140% of the 95th percentile or with a BMI of 120% of 95th percentile plus a serious comorbidity
- Obesity related comorbidities
  - o Type 2 Diabetes
  - o Hypertension
  - o Fatty liver disease
  - o Obstructive sleep apnea
  - o Hyperlipidemia
  - o Osteoarthritis
  - o Idiopathic intracranial hypertension

TYPES OF BARIATRIC PROCEDURES

There are several types of bariatric surgery, including sleeve gastrectomy (SG), adjustable gastric banding (AGB), Roux en-Y gastric bypass, (RYGB), and biliopancreatic diversion with duodenal switch (DS). The selection of surgery type depends on various factors such as the patient's BMI, medical history, and overall health, as well as patient choice. Bariatric surgery can be either restrictive (limiting the volume of the digestive tract, typically the stomach), malabsorptive (reducing the number of calories absorbed by the digestive tract), or a combination of both elements. The aim of surgery is to gain metabolic control and provide weight loss, resulting in resolution or delayed/arrested progression of obesity-related health conditions.

ADJUSTABLE GASTRIC BANDING (AGB)

Adjustable gastric banding involves placing a silicone band around the upper part of the stomach to create a small pouch. This restriction results in a delayed passage of food into the digestive tract. The band is connected to a port which is located underneath the skin. Fluid can be injected into the port to adjust the amount of restriction produced by the band on the stomach, thus restricting the amount of food that can be consumed. A laparoscopic approach (small incisions with use of video assistance) is

typical for placement, and the device can be removed if necessary in the future. Although the procedure is less invasive compared to sleeve gastrectomy or gastric bypass, it is less effective at achieving significant weight loss and resolution of obesity-related health conditions. Expected excess weight loss is 40-50%. Initial surgical risks are low, but reoperation rates can be as high as 40% due to malfunction or displacement of the band.

SLEEVE GASTRECTOMY (SG)

Sleeve gastrectomy (SG), also known as gastric sleeve or sleeve, has become the most widely utilized bariatric procedure worldwide. In the United States, sleeve gastrectomy accounts for approximately 57% of all bariatric procedures. SG is a procedure that involves removal of the lateral portion of the stomach (75-80%), resulting in a banana-shaped stomach. The diameter of the sleeve stomach is determined by a sizing tube to ensure consistency of the surgery. SG is highly effective at controlling or resolving obesity-related conditions such as type 2 diabetes and hypertension and at achieving significant weight loss. The procedure is restrictive, but it also lowers appetite by reducing the hunger hormone, ghrelin. Weight loss is steady over 12-18 months, and individuals are able to lose 50-70% of their excess weight. In comparison to bypass, the procedure is technically simpler with shorter operative time and involves no intestinal rerouting. Some patients prefer adjustable gastric banding over sleeve gastrectomy due to the irreversible nature of the sleeve. There is also an increased risk of surgical complications such as staple line leak (a serious complication), although the rate of leak remains low. A retrospective review of 1070 consecutive sleeve gastrectomy cases between 2012 and 2016 demonstrated a leak rate of 1-3% of cases. With certain techniques such as staple line reinforcement, oversewing of staple line, use of fibrin glues, etc., leak rates can be reduced to nearly 0%.

ROUX EN-Y GASTRIC BYPASS (RYGB)

Roux en-Y gastric bypass was first performed in 1954. The procedure involves creating a small (30-40 ml) gastric pouch by stapling off a small portion of the upper stomach and creating a connection directly to the jejunum of the small bowel. It is considered both restrictive (by creating a small gastric pouch, thus reducing food consumption) and malabsorptive (bypassing a portion of the proximal small intestine, thus decreasing absorption). Hormonal changes also lead to reduced hunger and improved blood sugar control. Prior to advancements in surgical techniques such as laparoscopic surgery and robotic surgery, the surgery was performed in an open fashion, resulting in higher complication rates. With advanced technology leading to fewer complications, however, the procedure has remained one of the most commonly performed bariatric procedures. RYGB is highly effective at achieving significant weight loss and resolution of medical comorbidities such as hypertension, type 2 diabetes, hyperlipidemia, and sleep apnea. As a result of bypassing a large portion of the intestine, there is a risk of vitamin deficiency, micronutrient malabsorption, loose stools and sarcopenia.

RGYB is typically reserved for patients with higher BMI levels and is a good option for patients suffering from gastroesophageal reflux (GERD). Patients can expect a 60-80% reduction in excess weight, with long-term weight maintenance with lifestyle adherence. Significant improvement or remission of type 2 diabetes is seen in 75-95% of patients. Lifelong compliance with vitamin supplementation and recommended diet is crucial to prevent complications such as nutrient deficiencies (iron, calcium, vitamin B12) and dumping syndrome (nausea, diarrhea after high-sugar meals). As with sleeve gastrectomy, there is risk of staple line leak; in addition, there exists additional potential long-term complications of bowel obstruction or ulcer formation. RYGB has a long track record with extensive supportive research.

ONE ANASTOMOSIS GASTRIC BYPASS (OAGB)

OAGB is a newer procedure similar to the RYGB; however, the gastric pouch is significantly longer and is then attached to a loop of jejunum. Often called the "mini" bypass, it is a faster and simpler procedure, involving a single anastomosis compared to the two anastomoses of the RYGB. The single anastomosis results in uninterrupted flow of bile and pancreatic enzymes from the duodenum. Excess weight loss is durable at 60-70%, with high rates of comorbidity resolution. Some concern exists regarding potential for significant bile reflux and the development of esophagitis and Barrett's esophagus. More time and research will be required to fully understand the long-term effects of the procedure.

BILIOPANCREATIC DIVERSION WITH DUODENAL SWITCH (BPD/DS)

DS, or "duodenal switch", is a complex bariatric surgical procedure that combines a sleeve gastrectomy and intestinal bypass. The surgery is both restrictive and malabsorptive, resulting in massive weight loss with resolution of most obesity-related health conditions. Due to changes in gut hormones, appetite is significantly reduced. DS differs from the RYGB in that the small bowel is transected just distal to the stomach (pylorus), allowing a more natural intake of food with reduced intake similar to sleeve gastrectomy. The intestinal bypass is more aggressive with the ileum being connected to the duodenum just distal to the pylorus at the transection site. A second anastomosis is created to allow integration of bile and pancreatic enzymes. Due to the significance of the intestinal bypass, the switch is reserved for patients with severe obesity and those with more severe medical comorbidities. Weight loss is significant with patients achieving 70-90% loss of excess weight, with sustained results at 5 years post-surgery. DS is highly effective at comorbidity resolution, with up to 99% improvement in type 2 diabetes. In a study of 350 super obese

adult patients, results of excess weight loss with DS were compared to RYGB. Percent excess weight loss was monitored up to 36 months post-op:

- 12 months – 64.1% DS vs 55.9% Bypass
- 18 months – 71.9% DS vs 62.8% Bypass
- 24 months – 71.6% DS vs 60.1% Bypass
- 36 months – 68.9% DS vs 54.9% Bypass

DS has recently increased in percent of bariatric cases performed due to its superiority to bypass in terms of weight loss and improved patient compliance. Similar to the RYGB, compliance with recommended lifelong multivitamins and post-operative diet is important to prevent complications of micronutrient and vitamin deficiencies.

SINGLE ANASTOMOSIS DUODENO-ILEAL BYPASS WITH SLEEVE GASTRECTOMY (SADI-S)

Single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) is a variation of the DS but with a single loop anastomosis rather than the two anastomoses seen with the standard DS. Weight loss is near-comparable to the DS with decreased operating times and risks such as intestinal obstruction. SADI-S provides optimal weight loss, significant improvements in obesity-related medical conditions, and lower risks for long-term nutritional deficiencies (such as vitamin and protein malnutrition) compared to the DS.

FINAL THOUGHTS

Weight loss surgery is not a cosmetic procedure—it is a metabolic intervention that can dramatically improve health and longevity for people with severe obesity. Each surgical technique has distinct mechanisms, benefits, and risks. The best option depends on individual health conditions, weight-loss goals, risk tolerance, and ability to commit to lifelong lifestyle changes.

A thorough consultation with a qualified bariatric surgeon is essential to determine the safest and most effective approach

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Comparing Outcomes

Procedure	Weight Loss	Diabetes Improvement	Nutritional Risk	Reversibility
Gastric Bypass	High	Excellent	Moderate–High	No
Sleeve Gastrectomy	Moderate–high	Very Good	Moderate	No
Adjustable Band	Moderate	Moderate	Low	Yes
BPD/DS/ SADI-S	Very High	Excellent	High	No

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The Plight in the Treatment of Obesity

by Bo Neichoy, MD

Evaluating patients for surgical treatment of obesity and weight-related issues has long been arduous. Misunderstandings about insurance, costs, and the constant ridicule faced by patients who need or undergo "weight loss surgery" have hindered therapeutic progress. To date, only about 1-2% of eligible patients ever consult a surgeon. A 2018 article in the journal Surgery for Obesity and Related Diseases highlighted this finding and was a rallying cry for better coverage. However, this number has not budged in two decades. I suspect this stems from widespread misconceptions about the surgery and its long-term benefits and risks. For many providers (and patients), weight loss surgery often is discussed as a "worst case scenario," without consideration of the long-term ramifications of associated comorbidities.

First, it's completely disruptive that we even call this "weight loss surgery." Worse still, we label it "bariatric" surgery—a term few know or can pronounce. It implies that the focus is solely on weight. I hope (but doubt) that the recent surge in GLP-1 medications has opened physicians' eyes to weight loss benefits. Numerous articles link GLP-1 meds to improvements in comorbidities like fatty liver, sleep apnea, arthritis, and diabetes. Yet, we overlook the fact that "weight loss" surgery delivers similar effects--only better and more sustainable. For instance, a November 2025 article in JAMA Surgery found bariatric surgery associated with 28.3% total weight loss versus 10.3% for GLP-1s, with lower ongoing costs (1). Another head-to-head study published earlier this year showed sleeve gastrectomy and gastric bypass linked to five times more weight loss than GLP-1 injections (2). Two large meta-analyses (both out of the Cleveland Clinic) reported that bariatric surgery reduced BMI more than GLP-1s (SMD -8.23), with lower risks of major adverse cardiovascular events (OR 1.50) (3,4). We will continue to see articles proving that weight loss surgery outperforms weight loss medications, while also decreasing long-term medical costs.

Past weight loss medications haven't taught us much. What happens when you stop them? We know the answer. Pharma anticipated that, spotting dollar signs: "You'll need it lifelong for results."

WHO QUALIFIES FOR WEIGHT LOSS SURGERY?

This is a loaded question! I break it into two conversations. First, insurance's view. The key issue is whether plans cover weight loss surgery as a benefit. It hinges on employers—and often their Third-Party Administrator (TPA). If employers are unaware of baseline costs for employee medical care, the benefit likely isn't included. For instance, if 25% of employees have diabetes, ideally you would weigh the ongoing care costs of diabetes against covering a surgery that could improve or resolve much of it—analyzed over 5-10 years. If you've negotiated employee benefits, you get it. However, bariatric surgery is still often listed under cosmetic benefits! The American Association of Clinical Endocrinology, the Endocrine Society, and the International Society of Endocrinology all recognize bariatric surgery as the best treatment for type II diabetes; however, no major insurance company recognizes weight loss surgery as a treatment for diabetes. Despite years of advocacy, it's not shaken the cosmetic stigma. What do you think a CFO or HR director says when asked about covering cosmetic surgery? For most employees, coverage dies there. It's not categorized under treatments for type II diabetes, sleep apnea, or fatty liver—though literature positions it as top-tier for these. For example, a large meta-analysis published in the Journal of Metabolic and Bariatric Surgery that covered 10 years found diabetes remission in 47%, sleep apnea in 85.7%, and hypertension in 61.7% of patient's post-surgery (5).

If it's not covered (as defined above), there's no chance of insurance approval. We often hear patients ask their doctors for letters of medical necessity. In 13 years, we've seen zero approvals from such notes!

For the 30% of the population with an insurance benefit that covers weight loss surgery, requirements typically include BMI 35-39.9 with a major comorbidity (type II diabetes, uncontrolled hypertension, cardiac disease, severe osteoarthritis, fatty liver, obstructive sleep apnea) or BMI 40+ (no comorbidity needed). No two plans match, and requirements vary. These don't align with current medical society recommendations: BMI 30-34.9 with comorbidity, BMI 35+ without issues, and over 27.5 for Asian populations (it's odd how other ethnicities were overlooked). These guidelines have been in place since 2022, but few insurers adopt them (mainly because Medicare hasn't).

Another hidden hurdle is that many employers impose separate co-pays or deductibles just for weight loss surgery. Imagine that for open heart or lung surgery (often lifestyle-related too)!

PAYING CASH

The second conversation arises when insurance denies coverage or when the patient does not have weight loss surgery as a covered benefit. Patients must then weigh their health's dollar value. The only

good news is that we do not have to deal with the pesky insurance rules. Insurers often mandate pre-op education timelines (e.g., 6 months with a dietitian). That can be a major barrier in the Panhandle of Texas—no one wants to take 6 half-days off work. Cash payers control the pace, easing the process and respecting their jobs. Free from insurance guardrails, we can discuss the benefits of surgery for every qualifying patient.

A unique challenge for patients paying cash for a surgery is medical tourism. I'd be surprised if you haven't seen a patient who underwent weight loss surgery in Mexico! On average, about 270,000 weight loss surgeries occur annually in the U.S. On the other hand, statistics show that 9.4% of Americans are morbidly obese (this would be about 32 million). I'm no mathematician, but the care gap is clear. Surgeons in Mexico perform 3-4 times more surgeries on Americans than do American surgeons. The exact figures are unknown, as there are no reporting guidelines for these patients. In 2017, we purchased a surgery center here in Amarillo to help drive down the overall cost of the procedure. Even with this price control, we'll never match Mexico's prices! The U.S. average cost for bariatric surgery is $20,000 vs. $6,500 in Mexico. Currently, the average cost in the Panhandle of Texas is $11,000, which by national standards is extremely competitive.

WHERE DO WE GO FROM HERE?

Patients hear every excuse against surgery:

- "I love you just like you are."
- "That's for 600-pound people."
- "Everyone regrets it."
- "You can't eat what you want after surgery."
- "You'll regain all your weight."

These statements ignore how patients feel (fatigued, depressed, physically/emotionally limited, in pain). They don't reflect real experiences or data. In the last decade, these procedures have become safer than most other major surgeries (joint replacement, cardiac, general surgery), with mortality rates under 0.1% and complication rates less than 5%. As gastric bypass wanes, safety profiles prove among the world's safest--and most scrutinized.

I urge patients, and their doctors, to consider how bariatric surgery fits into each patient's care pathway. I hope we all honestly consider what is the best for the patient. Not all patients will do great with surgery, but the overwhelming numbers prove that many more do well and add functionality back to their lives.

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Treating Obesity in Resource Limited Settings: A Comprehensive, Collaborative Approach

by Trey Bowen, MD

During a 3-month follow-up visit with one of my primary care patients at Heal the City, I asked what she thought contributed to the 12-pound weight gain and 2-point A1c increase since her last appointment.

"Since losing my job," she confided in me, "I haven't had enough money to buy what I know I should eat. It's too expensive to eat well." My patient felt that she had to choose between pursuing a healthy lifestyle and paying the rest of the required expenses to care for herself and her daughter. Her words highlighted the ironic challenges of combating obesity in a society in which a bag of broccoli can be more costly than a cheeseburger.

THE LINK BETWEEN OBESITY AND LOW SOCIOECONOMIC STATUS

My patient is not alone; many patients in our clinic have lamented about financial and social stressors crowding out their capacity to fully address obesity. In fact, multiple studies in the United States have identified associations between low socioeconomic status or food insecurity and increased risk of obesity; this link is clearest among women, children, and adolescents (1, 2). Multiple domains of daily life in a low-income setting undergird this complex relationship. For instance, limited means of transportation can pose a barrier to full-service grocery stores. Instead of surveying the produce section in such a store, people with transportation limitations may opt for the proximity of fast-food restaurants and convenience stores, making calorie-dense, nutrient-poor foods seem the more feasible option (2). Lack of transportation can also hinder access to workout gyms and safe public recreational spaces.

Other factors, such as education disparities, language and literacy barriers, lack of social support, and comorbid mental health conditions can limit a person's capability to steadfastly make optimal lifestyle choices (1). Even if patients with obesity have sufficient access to healthcare, the colossal cost of pharmacologic and surgical treatments leaves these interventions out of reach for low-income individuals, particularly for those without insurance. A study in 2017 even found that obesity may have a damaging effect on income (3); thus, these limitations can leave patients feeling trapped in a cycle of obesity and material poverty.

WEIGHT LOSS IS ACHIEVABLE IN LOW RESOURCE SETTINGS

Heal the City is a non-profit clinic that provides free primary care and referral services to uninsured patients in Amarillo and surrounding communities. Our organization serves those patients who are feeling trapped in cycles of chronic disease and who have nowhere else to go for their care. In time, we have learned that managing chronic disease requires more action than primary care visits and prescriptions. Instead, we have witnessed the importance of addressing socioeconomic limitations while continuing to provide evidence-based care. For the remainder of this article, I aim to emphasize many of

Heal the City's initiatives to combat obesity and to highlight additional resources that may be helpful for patients in other clinical settings. By employing a multidisciplinary team-based approach, collaborating with local partners, and connecting patients with outside resources, we can provide hope for patients with obesity who are navigating limited resources.

FOSTERING A COMPREHENSIVE, TEAM-BASED ENVIRONMENT IN THE PRIMARY CARE OFFICE

Our clinic serves patients through multiple departments, each aimed at providing support for specific social drivers of health. In addition to our primary care clinic and class-A pharmacy, our wellness center offers patients the opportunity to put recommended lifestyle changes into practice in a safe and supportive environment. Led by a certified personal trainer, the wellness center consists of weight-bearing exercise equipment, treadmills, stationary bikes, an exercise room, and an education classroom. Patients have the option to work out on their own or to perform the "workout of the day" designed by the personal trainer. We conduct several exercise classes each week, including yoga and dance-based aerobic classes. Some of our patients also choose to exercise at community gyms or budget-friendly workout facilities closer to their home.

In addition to physical activity resources, we offer multiple education classes a day, and many of the classes focus on dietary guidance, such as proper navigation of food labels. Another set of classes utilizes our on-site vegetable garden, equipping patients with skills to grow some of their own produce and helping them to experience whole foods from their source.

We have also found that activities promoting fellowship can cultivate enduring motivation in patients' health journeys. To illustrate, last year, our personal trainer led an 8-week weight loss group focused on guided diet and exercise interventions. The members' interactions with each other particularly impressed us: they readily shared their progress with one another and eagerly encouraged other members.

Along the same vein, our organization values celebrating patient accomplishments. Each Fall, we hold a banquet for patients, distributing accolades to celebrate their lifestyle efforts and health achievements. As I watch awardees beam and bring their extended family and friends to celebrate with them, I suspect that this event exerts a more profound impact on their weight loss journey than any recommendations I make during clinic visits.

Additional departments seek to address other components of obesity. The case managers meet with patients to identify challenges in social drivers of health, such as transportation challenges, food insecurity, or unpaid utility bills; they then work to connect patients with appropriate resources. The department has meticulously compiled a 32-page list of local resources to better connect patients with what they need.

Furthermore, our licensed professional counselors walk alongside patients with depression, anxiety, eating disorders, or other mental health challenges that are often comorbid with obesity. Even our dental department can have a positive impact on obesity – I have had several patients recount the negative effect of dental pain on the foods they can eat, followed by the new dietary opportunities after definitive treatment by our dental team.

COLLABORATING WITH LOCAL PARTNERS

While we are grateful to mobilize a passionate team of volunteers and staff to address the many facets of obesity, the support of community partners immensely enhances our efforts. For example, a registered dietitian from a local hospital has steadfastly conducted weekly individual dietary counseling sessions for several years. In addition, High Plains Food Bank supports patients in 3 invaluable ways. First, they supply meals for distribution to our patients twice a week. Second, they operate a meal program for elderly patients in our clinic, supplying nutrient-dense, low sodium frozen meals. Lastly, they offer live cooking demonstrations multiple times a week, using ingredients solely purchased from Wal-Mart to improve repeatability of the recipes in patients' homes.

These partnerships only scratch the surface of the community involvement in our patients' care. The financial contributions to the organization by individual donors and foundations, the volunteers sharing their expertise or gifts throughout all departments, the sub-specialists providing care at reduced or no cost, the hospital systems providing financial assistance – all of these exhibitions of generosity help our patients avoid having to decide between healthy lifestyles and access to healthcare. Addressing obesity in populations of low socioeconomic status requires an engaged and united community, and the Texas Panhandle demonstrates this approach well.

CONNECTING PATIENTS WITH NATIONAL RESOURCES

While local engagement is crucial for treating obesity, we have also connected patients with weight-loss promoting pharmacologic treatments. Non-profit organizations such as Direct Relief and Dispensary of Hope partner with charitable clinics and non-profit community health centers to open access to a vast array of medications, saving the health organizations millions of dollars every year. We have access to dulaglutide through this avenue. Moreover, pharmaceutical companies increase availability of medication through patient assistance programs. Staff in our pharmacy help patients navigate applications

for these programs, and eligible patients have no out-of-pocket cost. We are grateful to connect our patients with access to Ozempic through Novo Nordisk's patient assistance arm.

In addition to pharmacologic resources, providers can also pursue connections with "Food is Medicine" programs. These programs offer nutrition support, food "prescriptions," and medically-tailored meal and grocery services to patients with chronic disease. Other widespread resources include CDC's National Diabetes Prevention Program, as well as CDC's Family Healthy Weight Programs (4). These programs can connect families to free and low-cost education with both virtual and in-person learning opportunities. Our clinic employed the curriculum from the National Diabetes Prevention Program as the foundation for the new diabetes and prediabetes management program that we are piloting this year.

PERSISTING CHALLENGES, BUT ONGOING RESOLVE

Last year, 30% of patients with obesity who enrolled in our primary care program at the beginning of the year achieved a 5% decrease in body weight by December. While this feat testifies to their commitment and the above comprehensive approach, I remember the majority of patients with obesity who did not accomplish this metric, and I remember the deeply entrenched challenges that people of low socioeconomic status encounter on a daily basis. I remember that we cannot expect to overcome these difficulties quickly or simply. Rather, by continuing the slow, steadfast, collaborative, and comprehensive work to combat this complex disease, we can instill hope for our patients and equip them to manage obesity for life.

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Metabolic Associated Steatotic Liver Disease

by James Lusby, MD

It's 1980. John Lennon is killed in New York City. Mount St. Helens erupts. Al Michaels utters the immortal "Do you believe in miracles!" as the USA men's hockey team improbably triumphs against a favored USSR squad in the semifinals of the Lake Placid Winter Olympics. Are you old enough to remember these events? 1980 is also the year Ludwig and colleagues described the histologic features of a newly identified liver disease that, 46 years later, would be the world's most common chronic liver disease (1). Predictably, the rise of this new liver disease was associated with a rapid proliferation of inexpensive high calorie, ultraprocessed foods, decreased physical activity, and sedentary lifestyles that led to the rise of the obesity epidemic.

Non-alcoholic steatohepatitis (NASH) was the term used to describe this newly identified liver condition. It was categorized within a broader group of clinical/histologic diseases, termed Metabolic Associated Steatotic (fatty) Liver Disease (formerly NAFLD, now MASLD). MASLD encompasses a histologic spectrum, ranging from fat accumulation in hepatocytes without inflammation or fibrosis (simple hepatic steatosis), to hepatic steatosis with an inflammatory component that may or may be associated with fibrosis. The latter condition, referred to as Metabolic Associated Steatohepatitis (MASH), progresses to cirrhosis in up to 20 percent of patients. MASH is now recognized as a leading cause of cirrhosis (1,5). In my own practice, MASLD/MASH dominates as the cause of newly-diagnosed cirrhosis.

By definition, patients with MASLD alone have: fatty infiltration of the liver (>5% hepatic steatosis), at least one risk factor for metabolic dysfunction (obesity, hypertension, type 2 diabetes, and/or dyslipidemia), no other causes of steatotic liver disease, and minimal to no alcohol consumption. What is "minimal" alcohol consumption? One alcoholic drink has about 14 g of pure alcohol. Minimal alcohol use is <20 g daily for females and <30 g daily for males. This works out to about one alcohol drink per day for women and two for men.

This article will offer a brief overview of this liver disease, ubiquitous in modern medical practice. In particular, I will discuss the relationship of MASLD to the obesity epidemic that we are seeing in the US and around the world.

EPIDEMIOLOGY

MASLD is seen worldwide, with an estimated prevalence of 30 percent among the general population (2) The incidence appears to be increasing over time. In a meta-analysis of 63 studies including over one million individuals, the incidence of MASH increased from approximately 20 cases per 1000 person-years (in the year 2000) to 70 cases per 1000 person-years (by 2015) (3).

Patients with MASLD have at least one metabolic risk factor—obesity, type 2 diabetes, hypertension, or dyslipidemia. Predictably, if a patient has more than one of these risk factors, there is an increased risk for progression to MASH (4). While these metabolic factors are themselves linked to cardiovascular disease risk, it is uncertain if MASLD is independently associated with cardiovascular disease. Nevertheless, some studies suggest that MASLD itself is associated with coronary artery disease, arrhythmias, and heart failure (5).

Other conditions that have been associated with MASLD (independent of their association with obesity) include polycystic ovary syndrome, obstructive sleep apnea, chronic kidney disease, and previous history of cholecystectomy.

PATHOGENESIS

Why and how patients develop this disease has not been fully elucidated. The leading theory implicates insulin resistance as the key mechanism leading to liver steatosis and steatohepatitis (4). Other driving factors include an imbalance between energy intake and metabolic needs and systemic inflammation (5).

As with many other diseases with opaque causes, there are numerous other factors that may play a role in development of MASLD. Genetic factors, depletion of antioxidants, increased hepatic iron, and sleep apnea may have roles in specific patients (6,7). The ambiguous relationship between humans and their resident bacteria/fungi seems to be implicated in a litany of poorly understood diseases. MASLD is no exception. Intestinal microbes and changes in microbiome have been suggested by some to play a role in liver injury and development of MASLD (8).

CLINICAL FEATURES

When they present to my clinic, patients who ultimately are found to have MASLD often cannot explain the reason for their visit. They often report minor changes in labs or abnormal imaging of the liver as detected by their primary care provider. Hepatomegaly, fatty infiltration, or coarse appearance are common non-specific imaging abnormalities that need further consideration.

Most patients with MASLD are asymptomatic. Occasionally, patients complain of fatigue, malaise, or vague right upper quadrant discomfort.

At the other end of the spectrum are patients who present with new compensated or decompensated cirrhosis. Most patients with MASLD have no liver-related abnormalities on a physical examination, although some may present with hepatomegaly (enlarged liver) due to fatty infiltration of the liver. I find this challenging to determine on physical examination, especially in patients with obesity. Most often hepatomegaly needs confirmation by ultrasound or CT scan. Patients with MASH cirrhosis may have stigmata of chronic liver disease (palmar erythema, spider angiomata, ascites).

LABORATORY FINDINGS

Patients with MASLD may have mildly or moderately elevated liver enzymes (AST and ALT), although these labs may occasionally fall within normal limits. When elevated, the AST and ALT are typically two to five times the upper limit of normal, with an AST to ALT ratio of less than one, However, the degree of AST/ALT elevation does not predict the degree of liver inflammation or fibrosis, and a normal ALT level does not exclude histologic injury (9,10).

Alkaline phosphatase may be elevated by two to three times the upper limits of normal. Serum albumin and bilirubin levels are typically within the normal range unless the patient presents with cirrhosis. Patients who have developed cirrhosis may have other abnormalities such as low platelet levels and neutropenia. MASLD patients may have an elevated serum ferritin concentration or transferrin saturation; a serum ferritin greater than 1.5 times the upper limit of normal in patients with MASLD has been associated with increased risk of MASH and advanced fibrosis (11).

DIAGNOSTIC EVALUATION

When I evaluate a patient with suspected MASLD, my goals are to exclude other causes of liver disease and establish the diagnosis of MASLD.

MASLD may be suspected in patients who fulfill any of these criteria:

- Liver steatosis on imaging
- Unexplained elevation in liver enzymes (especially AST/ALT)
- Type 2 diabetes or two or more metabolic risk factors (dyslipidemia, obesity, hypertension, or insulin resistance/prediabetes
- First-degree relative of a patient with MASH cirrhosis

HISTORY AND PHYSICAL EXAMINATION

This includes a description of symptoms, existing medical conditions (type 2 diabetes, obesity, dyslipidemia, hypertension), family history, alcohol consumption (including amount, pattern, and duration of use), and medication use (including supplements and OTC drugs). Medications that have been linked to liver steatosis include amiodarone, glucocorticoids, methotrexate, and tamoxifen. The physical examination includes measurement of body mass index, as well as assessment for hepatomegaly and stigmata of chronic liver disease.

LABORATORY EVALUATION

For patients with suspected MASLD, I measure the following laboratory studies to assess liver function and to look for causative conditions: comprehensive metabolic panel (includes LFTs and glucose), CBC, PT/INR, glycoylated hemoglobin (A1c), serum total and HDL cholesterol and triglycerides, viral hepatitis panel, iron studies, IgG level, anti-mitochondrial, anti-nuclear and anti-smooth muscle antibodies, ceruloplasmin (in patients <50 years of age), alpha 1 antitrypsin (AAT) level, and anti-tissue transglutaminase antibody.

DIAGNOSTIC IMAGING

For patients with no recent liver imaging (within 12 months), I obtain a transabdominal ultrasound. In patients with MASLD, ultrasound often shows a hyperechoic texture (or "bright" liver) because of diffuse fatty infiltration. In a meta-analysis of 49 studies including 4720 patients, the sensitivity and specificity for ultrasound in detecting moderate to severe fatty liver were 85 and 94 percent, respectively, when using liver biopsy as the reference standard (13). However, the sensitivity appears to be lower in obese patients.

LIVER BIOPSY

Clinical, laboratory, and imaging findings are often adequate to establish a diagnosis of MASLD. Liver biopsy is typically reserved for patients if the diagnosis remains unclear or if an alternative etiology is suspected.

Histologic findings of patients with MASLD include any of the following:

steatosis alone, steatosis with lobular or portal inflammation without hepatocyte ballooning, and steatosis with hepatocyte ballooning but without inflammation. Liver biopsy remains the most accurate method for determining the severity of liver injury and inflammation, but it is limited by risk of biopsy-related adverse events (bleeding) and cost. The NAFLD activity score (NAS) histologic score is used to grade disease activity in patients with MASLD. It is a sum of the individual scores for steatosis, lobular inflammation, and hepatocellular ballooning.

For patients with MASLD plus another etiology of liver disease, interpretation of the liver biopsy can become more difficult. An opinion of a second pathologist or a specialized liver pathologist can be helpful.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of MASLD includes other conditions associated with liver steatosis, particularly for adult patients who do not have metabolic risk factors: alcohol associated liver disease, hepatitis C infection (genotype 3), Wilson disease, use of parenteral nutrition, drug-induced liver disease, and rare genetic diseases (usually these present in pediatric patients).

STAGING (EVALUATING FOR FIBROSIS)

After establishing the diagnosis of MASLD, patients should be staged to determine the severity of fibrosis (if present). For patients with MASLD who did not require a liver biopsy to establish the diagnosis, we typically evaluate for advanced fibrosis using ultrasound-based, vibration-controlled transient elastography (VCTE) to measure liver stiffness. We often refer to this test as a fibroscan in the office rather than the more accurate VCTE. This painless procedure involves placing a probe on the skin, sending vibrations through the liver. Results include a stiffness score measured in kilopascals (kPa) and a fat score (CAP). Higher kPa scores indicate more stiffness/scarring, while lower CAP scores mean less fat. Alternatives to VCTE include imaging with other ultrasound-based methods or with magnetic resonance elastography (MRE).

The FIB-4 index predicts advanced fibrosis by combining readily available laboratory values (platelet count, ALT, and AST) and age. The score from this formula provides a value that can help identify patients at risk of advanced fibrosis and cirrhosis.

TREATMENT

Lifestyle Modifications

Lifestyle modifications, including clinically significant weight loss by means of exercise and hypocaloric diet, are the cornerstones of treatment for MASLD and MASH. Patients should aim for a sustained weight reduction of at least 5% to reduce liver steatosis, 7 to 10% to reduce liver inflammation, and at least 10% to reduce liver fibrosis. When discussing diet and exercise, I stress the need for achieving energy balance in a patient's diet, rather than adherence to a specific diet or avoiding specific foods. Alcohol avoidance/cessation is mandatory.

Prescribing exercise as treatment requires education for most patients. I generally advise sedentary patients to begin walking with specific time intervals. Thirty minutes of uninterrupted walking, four times per week is my initial recommendation, if the patient can tolerate this from an orthopedic or cardiovascular standpoint. This should be increased to 45 minutes sessions 3-4 days per week if possible. If a patient has more experience, any form of cardiovascular exercise is beneficial.

I also stress the need to build strength while losing weight. Resistance training is not intuitive, and it is impossible to adequately educate a patient on this important intervention in the short span of an office visit. Fortunately, there are numerous free apps and online videos to demonstrate the basics of resistance training. If a patient has the resources, enlisting the help of a credible personal trainer is strongly encouraged. A cellphone with the free YOUTUBE app and trip to Walmart for a mat and some 5 and 10 lb. weights is all most patients need to get started. I advise full body resistance training on opposite days from the patient's cardiovascular activity of choice. Consistently beats motivation, and I advise the patients to view exercise and an energy balanced diet as side-effect free, cheap, highly effective medication. Despite the benefits, long term adherence to exercise and energy balanced diets is not always achievable. Thankfully there are now therapeutic drugs to address MASLD.

MEDICATIONS

There are now two FDA approved drugs to treat MASLD. The first drug approved, resmetriom (Rezdiffra) is a thyroid hormone receptor (THR) beta agonist for patients with coexisting moderate-to-advanced liver scarring (fibrosis) from MASH. As a THR-β agonist, it increases fatty acid breakdown (beta-oxidation), promotes lipid breakdown (lipolysis), boosts mitochondrial function, and lowers cholesterol production, all while avoiding harmful effects on the heart by sparing the cardiac THR alpha receptors. It addresses both the fat accumulation (steatosis) and the inflammatory components of MASH, leading to improved liver health. This drug is generally well tolerated, with diarrhea and nausea as the most common side effects.

In August of 2025, semaglutide (Wegovy) became the first GLP-1 agent approved for MASH-related liver disease. The drug was approved for MASH patients with advanced liver fibrosis but not cirrhosis. In the ESSENCE trial (15), 60% of patients on semaglutide achieved MASH resolution with no additional scarring compared to about one third on a placebo agent. The drug works by mimicking the natural hormone glucagon-like peptide-1 (GLP1), which regulates appetite and food intake by signaling the brain and by delaying gastric empty-

ing. This generally leads to patients eating less and losing weight. Thirty seven percent of patients in the ESSENCE trial had improvement in fibrosis/scarring. Nausea, vomiting, constipation and diarrhea are common side effects. Rarely, patients on this drug can be at increased risk for pancreatitis and thyroid tumors.

Diet and exercise inventions should be prescribed in conjunction with either of these drugs. Insurers require providers to perform the non-invasive tests (elastography/FIB-4) described previously in this article to identify those patients who likely have fibrosis and who are most likely to benefit from either of these therapies.

SURGERY

Bariatric surgery (Roux-en-Y gastric bypass and sleeve gastrectomy) has been associated with decreased steatosis, hepatic inflammation, and fibrosis in patients with MASLD. Before the development of medical therapy for MASLD, surgery was the primary option for treatment of this disease when lifestyle modifications failed. Individualized patient goals, available expertise, and personalized risk assessment must all be considered when considering surgical intervention for obesity and its complications.

CONCLUSIONS

MASLD is a multi-system disease that has become a pervasive problem worldwide. Liver biopsy should be avoided unless absolutely necessary for diagnosis. Diet and lifestyle modifications remain the cornerstones of management and potentially offer complete correction of the disease. The drugs resmetrion and semaglutide now augment lifestyle modifications for therapy of MASLD patients in whom testing suggests MASH/fibrosis. Challenges remain despite progress. The cost of the therapeutic agents may be an obstacle, and their duration of therapy remains uncertain. There are currently no liver-directed therapies for patients with MASH cirrhosis. Science continues to step forward to answer questions and provide new and innovative solutions to our current dilemmas in MASLD. Numerous promising metabolism-based drug therapies are being investigated, and early studies suggest effectiveness in treating not only fatty liver disease, but also some of its other metabolic complications. Randomized trials of agents, including drug combinations, to treat MASLD and MASH are eagerly awaited.

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Obesity Care in Context:
Why Person-Centered, Evidence-Based Nutrition Matters

by Amanda Ast, RD and Klemens Ast, RD

Obesity continues as one of the most pressing public health challenges in the United States. Current estimates indicate that over 40% of U.S. adults meet the criteria for obesity; increasing their risk of Type 2 diabetes mellitus, cardiovascular disease, and certain cancers, reducing their quality of life, and increasing all-cause mortality (1). Regardless of obesity's prevalence and consequences, care is often disconnected and influenced by misinformation.

This article outlines evidence-based approaches to obesity assessment and treatment, clarifies the unique role of the Registered Dietitian (RD), and emphasizes the importance of collaboration in a person-centered approach.

THE REGISTERED DIETITIAN: TRAINING, ACCOUNTABILITY, AND ETHICS

Registered Dietitians (RDs) are credentialed health professionals uniquely trained to provide Medical Nutrition Therapy (MNT). The RD credential is earned by completing an accredited graduate-level education program, practicing extensively under supervision, passing a national board examination administered by the Commission on Dietetic Registration (CDR), and engaging in continuing professional education (2).

RDs practice under established standards of care and ethics set by the Academy of Nutrition and Dietetics (AND) and are integral contributors to interdisciplinary care teams outlined in the American Diabetes Association (ADA) Standards of Care (3). This regulatory framework ensures accountability, evidence-based practice, and ability of the public to distinguish RDs from unregulated nutrition influencers or commercial wellness programs.

OBESITY AS A CHRONIC, RELAPSING DISEASE

Obesity should not be classified as a failure of willpower but as a chronic disease prone to episodes of relapse. Determinants of obesity may include several factors including: genetics, physiology, environment, psychosocial stressors, medications, and social determinants of health.

Due to the presence of excess adipose tissue in obesity, there is an increased risk of T2DM (4). Strong evidential support suggests that obesity management can delay progression from pre-diabetes to diabetes, while improving outcomes for those already diagnosed with diabetes (5,6).

Even modest weight loss, when sustained, is shown to improve glycemic control and cardiometabolic risk. A loss of 5-7% body weight was shown to improve A1c, blood pressure, and lipid markers, while a weight loss of greater than 10% body weight demonstrated the following disease-modifying effects: remission of T2DM and long-term improvement of cardiovascular outcomes (3,10,12). Invasive procedures, including metabolic surgery, often result in average weight loss exceeding 20%, which has been shown to be associated with reduced mortality and an improved quality of life (13,14).

ASSESSING WEIGHT AND HEALTH: BEYOND BMI ALONE

Body Mass Index (BMI), calculated as weight in kilograms divided by height in meters squared, remains the most widely-used screening tool for overweight and obesity. BMI categories include (3):

- Overweight: 25-29.9 kg/m2
- Obesity Class I: 30-34.9 kg/m2
- Obesity Class II: 35-39.9 kg/m2
- Obesity Class III: ≥ 40 kg/m2

While BMI is convenient and useful, limitations to the use of the model do exist. Since total body fat, fat distribution, and metabolic health issues are not factored into the model, individuals with high muscle mass or low lean mass may be mis-classified (15,16). In response, professional guidelines recommend confirming excess adiposity--when feasible--using additional anthropometric measures, including waist circumference or waist-to-hip ratio, particularly in individuals with a BMI between 25-34.9 kg/m 2 or at a lower BMI threshold when higher cardiometabolic risk factors are present (17).

In light of the ease of using the BMI method, coupled with the lack of competing methodology, BMI continues to be routinely used in U.S. clinical practice (18). Great person-centered care must begin when obtaining anthropometric data in a setting that values privacy and respect(3).

REDUCING WEIGHT STIGMA IN HEALTH CARE

Weight stigma--also referred to as fat or antifat bias--is prevalent among both the general public and healthcare professionals (19,20). The stigmatizing experiences encountered are associated with poorer health outcomes, an overall avoidance of future care, and the adoption of harmful health behaviors.

Healthcare professionals are encouraged to increase awareness of implicit and explicit weight bias with the adoption of person-first, nonjudgmental language. The Obesity Association of the ADA has published guidance on recognizing and addressing weight stigma, emphasizing empathy, and understanding the social complexity of obesity (21).

PERSON-CENTERED COMMUNICATION AND SHARED DECISION-MAKING

Conversations about weight management should be grounded in the principles of Motivational Interviewing. The first step is to align your care with the individual's goals and readiness for change (3,22). Health professionals should not assume that a person with overweight or obesity wants to address weight during a visit, particularly if the visit is for an unrelated concern.

Person-centered obesity care prioritizes shared decision-making, respect for autonomy, and individualized goal-setting (3,23). Treatment strategies may include nutrition therapy, physical activity, behavioral counseling, pharmacotherapy, medical devices, metabolic surgery, or a combination of approaches. The commonality of all of these strategies is that they must be tailored to medical history, life circumstances, and patient preferences.

NUTRITION, BEHAVIORAL THERAPY, AND PHYSICAL ACTIVITY: WHAT THE EVIDENCE SHOWS

Nutrition, behavioral therapy, and physical activity are foundational interventions for overweight or obese individuals, with or without a diabetes diagnosis (3).

Diet composition alone is not the determining factor in success. There is evidence supporting structured programs with frequent contact with the RD--often greater than sixteen sessions over the span of six months. With this number of visits, the RD completes a methodology referred to as the ADIME approach: nutrition assessment, diagnosis, intervention, monitoring and evaluation. In the "diagnosis" portion of ADIME, the RD creates individualized PES statements (Problem, Etiology, Signs/Symptoms), which are evidence-based, standardized, and designed to focus interventions on specific, resolvable issues.

Within the intervention and ongoing monitoring and evaluation, there is evidence that a plan creating a daily energy deficit of approximately 500-750 kilocalories (kcals) is successful for gradual, attainable weight loss (3). Going beyond diet intervention, the RD implements the long-term continuation of behavioral approaches such as Cognitive Behavioral Therapy (CBT) and motivational interviewing, which have increased success rates regarding self-efficacy, glycemic outcomes, and quality of life (22,26). A 2022 meta-analysis of randomized controlled trials found no meaningful long-term advantage of low-carbohydrate diets over carbohydrate-balanced diets for weight loss or A1c reduction in individuals with or without diabetes (24). The ability to sustain the lifestyle change, nutritional adequacy, and patient preference are better predictors of long-term outcomes. Long-term maintenance strategies are essential to prevent the common outcome of weight regain. The increasing use of non-regulated nutrition supplements and very-low-calorie diet plans are some of the causes for failure of weight loss/maintenance programs, due inability of the individual to maintain, as well as the increased risk of harm that may occur (12,25).

Physical activity should be part of a comprehensive weight management program. Physical activity level should be assessed and recommendations made, with the long-term goal of accumulating 30 minutes or more of moderate-intensity physical activity on most, and preferably all, days of the week, unless medically contraindicated. The RD is trained to create an individualized intervention and plan to implement physical activity goals. Movement goals need to be realistic and attainable, with consideration to lifestyle, cultural, and socioeconomic challenges.

THE UNDERUTILIZED ROLE OF THE REGISTERED DIETITIAN

Despite strong evidence and guideline recommendations, only a small percentage of individuals with obesity ever receive care from an RD. This gap persists despite universally-recommended referrals to RDs when initiating anti-obesity medications (26).

RDs are uniquely positioned to provide evidence-based nutrition counseling, behavioral support, and education that helps individuals evaluate critical diet misinformation, misleading product claims, and conflicts of interest prevalent in social media and commercial wellness spaces. RD services of MNT are covered by Medicare, Medicaid and private insurance companies. A referral is obtained by the care team (MD) to complete billable details, and to work jointly with the needs of the patient and patient care plan.

BUILDING SUSTAINABLE HEALTH, NOT JUST WEIGHT LOSS

Obesity-care extends beyond weight reduction. Building positive health behaviors, supporting psychological well-being, and improving quality of life are central goals of care. The ADA standards aim to increase success in obtaining these goals by emphasizing self-management support, Medical Nutrition Therapy (MNT), physical activity, psychosocial care, and ongoing re-assessment within a collaborative, person-centered model (3,27).

When obesity is addressed with compassion, evidence, and shared decision-making, outcomes improve. Registered Dietitians are essential partners in delivering ethical, effective, and sustainable obesity care--helping individuals move beyond diet culture toward lasting health.

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Obesity and Mental Health:
A Systemic, Social, and Psychological Disease

by Ruth Grant, MD

Over the past six decades, obesity rates in the United States have tripled, with approximately 40% of US adults (over 100 million people) now classified as obese (BMI ≥30) and nearly 10% meeting criteria for severe obesity (BMI ≥40) (1). Obesity is a chronic, progressive, and relapsing disease driven by complex interactions among biology, environment, behavior, and social determinants of health.

The physiologic consequences of obesity are extensive and affect all eleven major organ systems. Cardiovascular complications include hypertension, coronary artery disease, myocardial infarction, and stroke (2). Respiratory consequences include obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (3). Endocrine and metabolic disturbances—particularly type 2 diabetes, dyslipidemia, and metabolic syndrome—are tightly linked to excess adiposity and chronic inflammation (4). Musculoskeletal complications such as osteoarthritis, chronic joint pain, and reduced mobility significantly impair physical functioning and quality of life (5).

Obesity also adversely affects reproductive and hormonal health, increasing the risk of polycystic ovary syndrome (PCOS), infertility, and pregnancy complications in women and lowering testosterone levels in men (6). Dermatologic manifestations include intertrigo, acanthosis nigricans, skin tags, delayed wound healing, and increased susceptibility to cellulitis (7). Urologic complications include urinary incontinence, nephrolithiasis, and recurrent infections (8). Gastrointestinal sequelae include GERD, gallstones, pancreatitis, diverticulitis, and metabolic-associated fatty liver disease, which may progress to cirrhosis (9). Obesity impairs lymphatic function and compromises immune response (10). It is also associated with neuropathy and increased risk of neurodegenerative disorders such as Alzheimer and Parkinson disease (11). It also increases the risk of at least 13 cancers (meningioma, thyroid, esophageal, breast, ovarian, endometrial, colorectal, kidney, liver, gallbladder, pancreatic, and multiple myeloma) (12). Severe obesity shortens life expectancy by 5–20 years (13).

Despite this extensive physical burden, the psychiatric consequences of obesity have historically been under-recognized. Obesity is strongly associated with depression, anxiety, emotional dysregulation, and disordered eating (14). These psychiatric conditions are not merely consequences of obesity—they also contribute to its persistence by impairing motivation, reward processing, sleep, and behavioral regulation. Obesity and mental illness thus form a self-reinforcing, bidirectional cycle.

OBESITY, SLEEP APNEA, AND DEPRESSION

One of the most significant links between obesity and mental illness is obstructive sleep apnea. Obesity is the strongest modifiable risk factor for OSA, a disorder characterized by recurrent upper airway collapse, sleep fragmentation, intermittent hypoxia, and impaired executive functioning (15). OSA independently increases the risk of depression, with odds approximately doubled in mild disease and rising to nearly threefold in moderate to severe OSA (16). Chronic sleep disruption alters emotional regulation, increases inflammatory signaling, and impairs neurotransmitter systems involved in mood and reward (17).

Importantly, OSA is a reversible contributor to psychiatric morbidity. Although short placebo-controlled CPAP trials did not demonstrate immediate mood improvement, sustained CPAP therapy consistently reduces depressive symptoms, improves cognition, and enhances overall quality of life (18). Treating sleep disorders is therefore a foundational component of mental health care in individuals with obesity.

TREATMENT BURDEN, POLYPHARMACY, AND ECONOMIC STRESS

Obesity is closely associated with multimorbidity, resulting in high rates of polypharmacy. Nearly 20% of adults with obesity take five or more prescription medications, compared with 9% of normal-weight adults (19). As medication burden increases, adherence declines due to cost, side effects, cognitive overload, and treatment fatigue—factors that are further amplified by depression and anxiety.

The economic burden of obesity compounds these challenges. Adults with obesity incur approximately $1,861 more annually in total medical costs, with excess costs exceeding $3,000 per year in severe obesity (20). Workplace discrimination further intensifies financial strain. Weight bias in hiring, promotion, and compensation is well documented; obese men earn 5–10% less and obese women 5–15% less than their thinner peers, despite similar qualifications (21). Lower lifetime earnings restrict access to health care, nutritious food, and mental health services, reinforcing stress and depressive vulnerability.

CHILDHOOD OBESITY AND BULLYING

The psychological consequences of obesity often begin early. Children and adolescents with obesity are up to three times more likely to experience bullying, teasing, and social rejection (22). These experiences are strongly associated with depression, anxiety, substance use, school avoidance, and suicidal ideation (23). Fear of harassment leads an estimated 160,000 children to skip school daily, demonstrating how obesity-related stigma creates long-term harm beginning in childhood (24).

POVERTY, STRESS, AND DEPRESSION

Obesity disproportionately affects individuals living in poverty, where food insecurity, unsafe environments, limited access to healthy foods, and chronic financial stress promote metabolic dysregulation (25). Persistent activation of stress pathways increases visceral fat accumulation and inflammation, while heightening vulnerability to depression (26). Depression, in turn, impairs behavioral regulation and motivation, perpetuating weight gain.

Together, sleep disruption, inflammation, stigma, treatment burden, discrimination, and socioeconomic stress converge to place individuals with obesity at uniquely high risk for chronic mental illness.

BREAKING THE CYCLE: TREATING OBESITY TO IMPROVE MENTAL HEALTH

Because obesity and mental illness are biologically and behaviorally intertwined, effective treatment of obesity often leads to parallel improvements in psychological well-being.

WEIGHT-LOSS MEDICATIONS

Modern anti-obesity medications—particularly GLP-1 receptor agonists—have transformed obesity treatment. Clinical trials demonstrate that:

- Semaglutide produces average weight loss of 12–15% of total body weight over 12–18 months (27).
- Tirzepatide, a dual GLP-1/GIP agonist, results in 18–22% average total body weight loss, with some patients achieving over 25% (28).

These levels of weight reduction are associated with improvements in insulin resistance, blood pressure, inflammatory burden, mobility, and sleep apnea severity. For many patients, medication-assisted weight loss leads to improved mood, self-esteem, body image, and social functioning by reducing stigma and physical limitation (29).

However, these medications are not psychologically neutral. Because they act on central appetite and reward pathways, some individuals experience anxiety, irritability, emotional blunting, or mood changes (30). Appetite suppression may exacerbate restrictive eating patterns in those with eating disorder histories, and rapid weight loss can produce identity shifts or fear of regain (31). Mental health screening and ongoing monitoring are therefore essential components of pharmacologic obesity treatment.

BARIATRIC SURGERY

Bariatric surgery remains the most effective long-term intervention for severe obesity. Typical outcomes include:

- Gastric bypass: approximately 25–35% total body weight loss (32)
- Sleeve gastrectomy: approximately 20–30% total body weight loss (33)

Beyond weight reduction, bariatric surgery induces hormonal and inflammatory changes that improve satiety, insulin regulation, and metabolic stability (34). Numerous studies demonstrate substantial reductions in depression and anxiety and marked improvements in quality of life following surgery (35).

EXERCISE AND LIFESTYLE INTERVENTIONS

Physical activity remains one of the most powerful nonpharmacologic interventions for both obesity and depression (36). Exercise improves sleep quality, reduces stress hormones, enhances dopamine and serotonin signaling, lowers inflammation, and strengthens self-efficacy (37). Importantly, its antidepressant effects occur even in the absence of significant weight loss (38)

CONCLUSION

Obesity is not merely a metabolic disorder; it is a systemic disease with profound psychological, social, and economic consequences. The bidirectional relationship between obesity and mental illness creates a reinforcing cycle that affects individuals across the lifespan. Effective treatment requires integrated, patient-centered care that addresses sleep disorders, metabolic health, mental health, stigma, and socioeconomic barriers simultaneously. By treating obesity comprehensively, clinicians can improve not only physical health outcomes but also emotional well-being and quality of life.

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GLP-1 Agonists and Their Impact on Mental Health

by Cesar Cardenas Jr, MD, Assistant Professor, Department of Psychiatry, TTUHSC, Aliya Khan MS3, TTUHSC, Suyash Srivastava MS3, TTUHSC

The introduction of GLP-1 agonists has enabled an improved pharmacological approach to overcoming obesity. These "miracle weight loss" medications have helped those who previously had difficulty losing weight. The success of these medications in treating obesity has enabled further research into broadening their indications for other disorders. Specifically, the GLP-1 agonists have been hypothesized to help with issues in mental illness. As these medications become mainstream and the threshold for their use lessens, it's important to be aware of possible adverse effects/complications. There has been concern that GLP-1 agonists can affect mental health and/or increase the risk of suicide. This article will address these issues and will also examine the psychiatric adverse effects of these medications.

PSYCHIATRIC TOLERABILITY

With the increased usage of GLP-1 agonists, it is important to monitor any effects on mental health--specifically, in those who are obese and who have co-morbidities such as depression, anxiety, formal thought disorder, or bipolar disorder. In recent studies, these medications appear to be well tolerated. Bak et al. conclude that the addition of a GLP-1 "does not increase the severity of psychopathology" (1). Other studies have observed similar outcomes, especially the review by Giorgi et al., which confirmed their safety and stated that "very few studies" reported worse psychiatric outcomes associated with these medications (3).

TREATING ANTI-PSYCHOTIC-INDUCED WEIGHT GAIN

Due to the observed psychiatric tolerability of these medications, one suggested use of GLP-1 agonists in psychiatric practice is in the adjunctive treatment of anti-psychotic induced weight gain (AIWG) and metabolic dysregulation. In a 2024 systematic review of AIWG, Bak et al showed that liraglutide produced a mean weight loss of -4.7 kg (95% CI -4.85 to -4.56; $p<0.001$), while exenatide produced a mean weight loss of -2.48 kg (95% CI -5.12 to 0.64; $p=0.07$) (1). Importantly for clinicians, the review noted that exenatide and liraglutide did not adversely affect psychopathology within their included studies (1).

From a clinician's perspective, this matters because not only is obesity a cardiometabolic risk factor, but it can also hinder recovery from mental illness. The concern about weight gain can be a deterrent when discussing or continuing antipsychotic medications, especially in those with metabolic co-morbidities. The 2024 review explicitly links obesity to reduced quality of life and emphasizes that, in severe mental illness, obesity can "hamper recovery and social participation" (1). Although GLP-1 agonists are not first-line agents in the treatment AIWG, further trials hold promise that they will be safe and effective in the management or prevention of AIWG.

IMPROVED PATIENT-REPORTED WELL-BEING

Beyond weight loss alone, a review by Osborne and Abdelgadir reports several trials in which GLP-1 agonist interventions improve patient-reported measures of well-being. One trial by Gudzone et al. noted "improvements in psychosocial function and a decrease in depressive symptoms in patients treated with tirzepatide at various doses" (5). While few studies compare various weight-loss medications, a meta-analysis by Liu et al. found that tirzepatide showed the greatest improvement in the Impact of Weight on Quality of Life-Lite score (5).

These summaries suggest a clinically relevant pattern: for some patients, weight loss and improved physical functioning may coincide with improved psychosocial functioning and mood. Furthermore, GLP-1 agonists have the potential to replace the current gold standard of bariatric surgery. Desired weight loss requires a multifactorial approach. Finally, inability to lose weight can take a psychological toll on individuals. Although GLP-1 agonists have not demonstrated equivalent effectiveness to antidepressants for clinical depression, there is potential for their improvement in the quality of life/well-being in this patient population.

DIRECT PSYCHIATRIC USES

GLP-1 agonists are currently being studied for their use as novel treatments for psychiatric and neurocognitive disorders. Animal studies report potential benefit of GLP-1 agonists for use in various dementias, including Parkinson disease (3). Multiple preclinical studies propose a possible mechanism by which GLP-1 agonists would provide neuroprotective and anti-inflammatory benefits.

Other avenues being explored are their use for the treatment of substance use disorders. Several studies investigating GLP-1 agonists in rats found a decrease in alcohol use, with similar findings having been observed for opiates, cocaine, and nicotine use disorders (3).

In addition, since GLP-1 receptors are found in the central nervous system, there is a possibility that they can be used for other common psychiatric disorders. Several studies have investigated the effect of GLP-1A on mood and anxiety disorders, but the evidence is mixed, and further study is warranted (3). A small number of studies have examined the role

of GLP-1A on eating disorders such as binge eating disorder with comorbid obesity, but the amount of research is limited, and results are mixed (3).

SURVEILLANCE FOR ADVERSE EFFECTS

GLP-1 receptor agonists have revolutionized the management of obesity, but it is crucial to highlight several important drawbacks.

The FDA's adverse event reporting system database has shed light on the side effects of GLP-1 agonists. Recently published data reported adverse effects from the first quarter of 2004 up to the first quarter of 2023. The median time to onset of related adverse effects was 31 days (2). The most common adverse effects are gastrointestinal, such as nausea, vomiting, diarrhea, and constipation. These gastrointestinal side effects—sometimes severe--can impact the mental well-being of patients taking these medications. Psychiatric adverse events unrelated to physical symptoms have also been reported, including nervousness, stress, eating disorders, fear of injection, self-induced vomiting, binge eating, and fear of eating. Of 181,238 adverse events reported from 2004 to 2023, 8,240 were psychiatric adverse events (i.e. about 4.55%). The breakdown by GLP-1 agonists is the following: 3,948 for exenatide, 1,152 for liraglutide, 12 for lixisenatide,1,833 for dulaglutide, 1033 for semaglutide, and 252 for tirzepatide (2).

SUICIDAL RISK

A concern has been raised about the use of weight reduction medications and increased risk of suicidal ideation. In 2023, the European Medicines Agency became aware of potential links between GLP1 agonists and suicidal ideation after receiving approximately 150 reports of concern (4). Since this report, several randomized controlled trials and retrospective cohort studies have looked closely at the risk of suicidal ideation with these medications. Recently published data of randomized control trials did not identify indicators of suicidality with GLP-1s, and retrospective cohort studies indicated a neutral or reduced impact of GLP-1 on suicidal ideation (4). In addition, no increased risk of suicidal ideation was found when compared to SGLT-2 inhibitors used in individuals with T2DM and obesity in a study by Hurtado et al. Reinforcing this observation, retrospective studies utilizing data from Sweden, Denmark, and the United Kingdom have revealed consistent findings on suicidal ideation (4). At the present time, the FDA has requested that manufacturers remove warnings about suicidal thoughts or actions from the package inserts, although they still advise that practitioners monitor their patients for depressive symptoms or suicidal thoughts, with the decision to discontinue medications if suicidal ideation occurs.

In summary, the introduction of GLP-1 agonists and their use have been highly successful in treating obesity. These medications also have the potential for use to combat antipsychotic-induced weight gain and possibly to treat psychiatric illnesses, including various substance use disorders and mood/anxiety disorders. In addition, they appear not to exacerbate overall psychiatric illness. Initial concerns for risk of suicidal ideation by these medications have also been studied, with multiple randomized controlled trials and retrospective cohort studies demonstrating a reduced or neutral impact on suicidal ideation. As further research contributes to understanding of the role of GLP-1 receptors in the central nervous system, there appears to be future potential for their expanded use in psychiatric and neurocognitive disease.

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The Insidious Role of Obesity on Human Reproduction

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"…fatness and flabbiness are to blame. The womb is unable to receive the semen, and they menstruate infrequently…" Hippocrates (460-370 BCE)

Obesity has been recognized as an obstacle to successful reproduction since antiquity. In 2003, Panhandle Health published my manuscript entitled "Reproductive Consequences of Obesity: Big Mothers, Big Babies, and Big Consequences". Since that time, the obesity epidemic has only worsened. At the TTUHSC-Amarillo Infertility Clinic, the median BMI of an infertility patient between 1999-2002 was 30.4 kg/m2 (95% CI 29.6-31.2), and, by the end of 2025, the median BMI had increased to 34.4 kg/m2 (33.5-35.0). Over the past 25 years, 70% of women presenting to this clinic are obese. Among Hispanic women, the rate is 73% (unpublished data).

Twenty-three years after the first survey of obesity in the Amarillo infertility clinic, it is concerning that infertile women living in the Panhandle are becoming more obese and less healthy. Fertility disorders associated directly or indirectly with obesity overshadow all other established causes of infertility (including tubal disease, endometriosis, and male factors).

Obesity is not limited to the Texas Panhandle. In 2018, the incidence of obesity among American men and women was 43% and 42%, respectively--a dramatic increase from 22.9% among the general US population 25 years ago (1). Among American women, 11.5% are classified as severely obese (BMI > 40 kg/m2) (1). A sharp increase in childhood obesity during this interval has been particularly alarming. Ethnic disparities also exist, with 57% of African American women and 44% of Hispanic women now classified as obese (1).

Obesity plays a major contributory role to the pathophysiology of ovulatory disorders and endometrial function, and obesity and insulin resistance are major risk factors for endometrial cancer. Obesity correlates negatively with natural conception rates, infertility treatment success (including in vitro fertilization (IVF), infertility treatment safety, and uncomplicated obstetrical outcomes (2). Obesity conveys a multifactorial "dose-dependent" negative effect on male and female reproductive function, leading to disruptive neuroendocrine regulation, insulin insensitivity, dysregulated adipokine production, inflammation, oxidative stress, and epigenetic changes (3). Furthermore, successful reproductive outcomes among obese women appear to potentiate obesity in future generations

Herein, obesity will be defined as a BMI ≥ 30 kg/m2, although this definition is imperfect and does not take into consideration fat distribution (central obesity is associated with greater metabolic risk). There is only a paucity of information correlating relative fat mass (RFM), a newer and better obesity metric, with infertility (4). In this paper, the adverse effects of obesity on reproduction in men and women will be reviewed. Treatment options (weight reduction by lifestyle modification, pharmacological management, and bariatric surgery) and reproductive outcomes will also be summarized. Once pregnancy has been accomplished, the dilemma is not resolved, as obese pregnant women remain at risk for a variety of obstetrical complications compared to lean counterparts (Table 1) (2). That discussion is beyond the scope of this paper.

Table 1. Reproductive and obstetrical conditions associated with obesity.

Ovulatory dysfunction
Diminished oöcyte quality
Altered endometrial receptivity
Diminished semen quality
Increased time to fertility
Depression
Sexual dysfunction
Miscarriage
Stillbirth
Gestational diabetes
Preeclampsia
Fetal macrosomia
Fetal growth restriction
Cesarean section
Wound infection
Venous thromboembolism

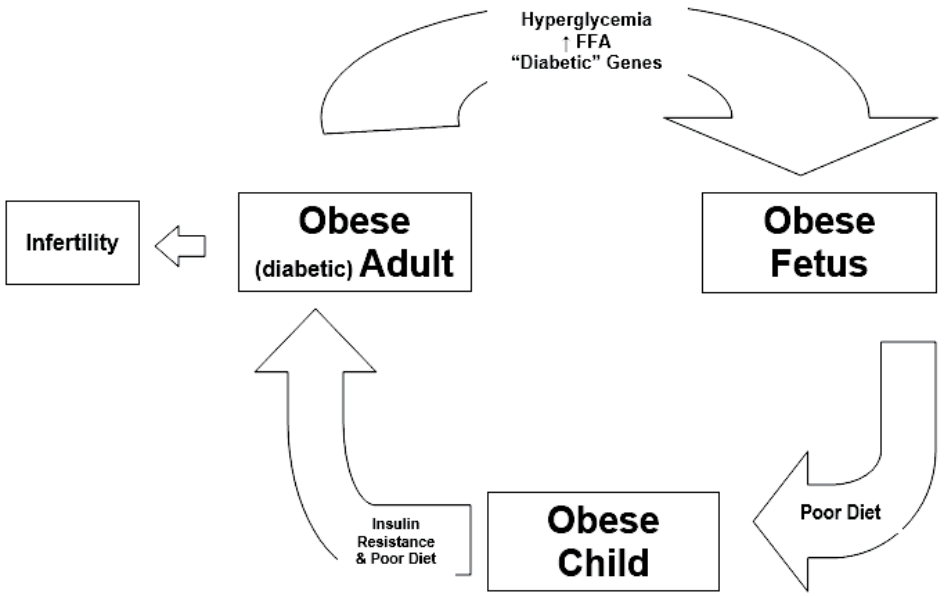
WOMEN: ANOVULATORY INFERTILITY

During the reproductive years, an ideal BMI (20-24.9 kg/m2) is associated with the highest reproductive success. In studies of women who are overweight (BMI 25-29.9 kg/m2) or obese, there is a three-fold increased relative risk of anovulatory infertility compared to lean individuals. A linear relationship exists between anovulatory infertility and advancing adiposity (particularly central obesity) in adolescence and adulthood (3,5,6). Even obesity in childhood (age 7) is an independent predictor of ovulatory dysfunction at age 33 (7). This finding suggests that genetic, epigenetic, and metabolic programming has already

occurred by childhood, and indeed, the intergenerational origin of obesity begins following conception (8). (see Figure 1) It is noteworthy that the presence of polycystic ovary syndrome (PCOS), a condition that is exacerbated by obesity, is a separate entity--but admittedly could confound studies of obesity on fertility (2,9).

The principal pathophysiological cause of obesity-induced ovulatory dysfunction is complex with the following components implicated: disruption of the hypothalamic-pituitary-ovarian axis, relative insulin resistance with stimulation of ovarian testosterone formation, a fall in sex hormone binding globulin, and changes in adipocytokine concentration and function (2,10,11).

Figure 1. Inter-generational pathway to obesity.



WOMEN: OÖCYTE AND ENDOMETRIAL DYSFUNCTION

Fecundability, the probability of a woman conceiving within a given interval, is reduced in obese women (2). This finding holds true even in obese ovulatory women. Alterations in normal folliculogenesis is more common in the obese, leading to poor oöcyte quality. Specifically, disruption of the meiotic spindle formation and aberrations in mitochondrial function have been described. These developmental defects persist even when ovulation has been induced, explaining the lower pregnancy rates in obese women who undergo successful ovulation induction (12).

The endometrium of obese women exhibits impaired receptivity to blastocyst implantation, contributing to implantation failure and elevated rate of miscarriage (13). Even assisted reproductive technologies do not adequately compensate for these defects. IVF cycle cancellation, fewer and poor oöcyte quality per retrieval, and lower live birth rates characterize IVF cycles performed on obese women (2).

WOMEN: MISCARRIAGE

Although there is some disagreement in the literature, most studies support increased miscarriage rates in obese women (2). Mechanisms for this association include thyroid dysfunction, insulin resistance, leptin resistance, mental health comorbidities, obesity-associated inflammation, and implantation failure (14,15). Obese women undergoing IVF also have higher rates of miscarriage compared to normal controls with odds ratios reported between 1.46-1.75 (2). Although the most common cause for pregnancy loss is aneuploidy, obesity is associated with a higher euploid miscarriage rate (58%) compared to women without obesity (37%) (16).

MEN

A male factor may be found in as many as 50% of infertile couples. Obesity is distinctly associated with reductions in semen quality. Impaired semen parameters (low semen volume, low total motile sperm count, abnormal motility/viability, and abnormal sperm morphology), and hormonal dysregulation have been directly associated with obesity (2,11,17). Obesity also correlates with sleep apnea and erectile dysfunction (18).

Among obese reproductive age men, disruption of the hypothalamic-pituitary-testicular axis and extragonadal production of estradiol in the fat cells contribute to higher estradiol production, lower free and total testosterone, and lower testosterone/estradiol ratios (19). In addition, inhibin B, a marker of Sertoli cell function and spermatogenesis, is often decreased. Finally, increased adiposity raises scrotal temperature, further impairing spermatogenesis. Chronic inflammatory factors lead to oxidative stress that damages testicular and epididymal tissues (20). Oxidative stress leads to sperm DNA fragmentation and reduced fertilization capacity (2,20). Obesity in men is associated with lower live birth rates after IVF, with a reported odds ratio of 1.69 compared to healthy men (2,10).

DOUBLE TROUBLE: THE OBESE COUPLE

Often, both partners in an infertile marriage are obese. This presents additional concerns, as infertility rates ae higher when both partners are heavy compared to couples where only one or neither is obese (2,10). A higher risk for pregnancy loss also exists (10). From a counseling viewpoint, it is worthwhile

to have both partners present for the initial infertility consultation to discuss procreative ramifications of the "obese marriage".

TREATMENT

Weight loss is the ultimate goal for infertility complicated by obesity. Successful weight reduction strategies are associated with higher pregnancy rates, shorter interval to pregnancy, lower incidence of miscarriage, and favorable obstetrical outcomes. Even though confounding factors plague studies of weight loss and fertility, multiple analyses have concluded that the relationship between weight loss and pregnancy rates (spontaneous and assisted) is not a linear relationship. In other words, weight loss among the obese does not convey pregnancy rates comparable to those in lean individuals who have never been overweight (2,22,23). This finding supports a multifaceted interplay of genetic and environmental factors necessary for successful reproduction (20,24).

In men, weight loss tends to be associated with improved serum testosterone levels, but the effect on spermatogenesis is less definitive (2,19,23). Weight loss in women improves rates of spontaneous and medically-induced ovulation (2,23).

SPECIFIC TREATMENT: LIFESTYLE MANAGEMENT

Weight loss through good dietary and exercise habits remains the foundation for the treatment of obesity in men and women. Even 5% weight loss may improve insulin sensitivity and diminish androgen production (and occasionally restore ovulatory function) in women with PCOS (26). PCOS is a distinct entity from obesity and not all women with PCOS are obese. One randomized control trial in obese infertile women (without PCOS) has concluded that metabolic improvement achieved through lifestyle changes alone does not meaningfully improve fertility rates or birth outcomes (27).

On the average, vigorous exercise results in 2-4% weight loss over a year and may be best suited for maintenance (28). Weight loss by caloric restriction is slow and non-linear, and sustained compliance is challenging (29). Metabolic counterregulatory mechanism may hinder weight loss (22). A few obese individuals may be motivated by infertility alone to sustain a healthier lifestyle and lose significant weight that can be instrumental to better reproductive outcomes.

Meta-analysis data support rigorous, structured, face-to-face preconception programs involving 10 or more sessions and allied with specific weight loss goals. These comprehensive and intense programs, primarily offered in Australia, do result in additional pregnancies compared to traditional intervention of a single office counseling session (odds ratio 2.17 (95% CI 1.21-3.86, p = 0.004)) (29). This type of program may work best in countries like Australia and New Zealand that discourage or limit infertility treatment in the moderate-severely obese population until the BMI is < 35 kg/m2 (30).

SPECIFIC TREATMENT: PHARMACOLOGIC MANAGEMENT

Weight loss medications may be offered when lifestyle changes alone are unsuccessful. Most anorectic and other weight loss medications (except orlistat and metformin) are relatively contraindicated during pregnancy, so effective contraception should be stressed during the weight loss phase. If no contraception is elected, the weight loss medication should be discontinued as soon as pregnancy is diagnosed.

GLP-1 and GIP receptor agonists have achieved the best results among weight loss medications, and recent studies support use prior to pregnancy (31). Ovulation and pregnancy rates are higher after weight loss with GLP-1 receptor agonists in obese women and those with PCOS. In obese women, this drug class suppresses inflammatory cytokine production, enhances vascularization, and reduces oxidative stress at the site of embryo implantation (32). These findings raise the question of whether pregnancy loss rates will be positively affected by pre-pregnancy use of GLP-1 receptor agonists.

In the obese male, GLP-1 receptor agonists hold promise, as early data demonstrates normalization of the hypothalamic-pituitary-testicular axis and gonadal testosterone production, with improved semen parameters (33). In non-obese men, no effect on sex steroid production or semen parameters has been demonstrated, supporting the observation that loss of body fat is the cause of improved fertility and not the drug itself (34).

SPECIFIC TREATMENT: SURGICAL MANAGEMENT

Bariatric surgery remains the most effective intervention for significant and sustained weight loss, although its role as a primary modality may be diminishing with the advent of new pharmacological modalities. Surgery also carries perioperative and postoperative risks to the patient that must be balanced against the benefits of weight loss. Compared to GLP-1 receptor agonists, weight loss is more durable with bariatric surgery, as weight re-gain is common following cessation of drug therapy (35,36). Combination therapy may be an answer in some individuals (37).

Case-control studies have shown improvement in pregnancy rates after bariatric surgery, particularly with PCOS, but there is limited data from higher quality studies in the morbidly obese on reproductive outcomes and especially pregnancy outcomes (2,36). Delaying pregnancy for 12-18 months after surgery is recommended to avoid nutritional deficiencies during pregnancy. During subsequent pregnancy, micronutrient supplementation is recommended due to malabsorption, especially after Roux-en-Y procedures (38).

There has been only limited study on male fertility following bariatric surgery, since the primary indication for surgery is limited to chronic conditions like type 2 diabetes, hypertension, and cardiovascular disease. Nevertheless, testosterone level and sexual function do improve following bariatric surgery in men (39).

DO WEIGHT LOSS AND INFERTILITY TREATMENTS POTENTIATE THE OBESITY EPIDEMIC?

The incidence of obesity has ballooned over the past century to the point that half of American women are overweight or obese at the time of conception (40). Several explanations have been offered to explain this troublesome trend, perhaps the most pervasive being an inactive lifestyle and dietary habits favoring obesity. Another factor may be in play – abolition of the natural selection process against reproductive success in obese women by infertility treatments. This hypothesis may well explain to some extent the increasing levels of diabetes type II and PCOS in developed countries. It is likely that future developments in pharmacology will be able to counter the effects of iatrogenic proliferation of obesity-related genes. Gene editing by CRSPR remains another potential treatment but will require further safety studies and ethical deliberation (41).

UNANSWERED QUESTIONS

- What is the optimal weight, BMI, or percent weight reduction for reproductive success in the obese patient?
- Do racial or gender differences exist?
- Even after normalization of body weight in the morbidly obese, why do discrepancies in fecundity persist?
- Should pharmacologic or surgical treatment be offered sooner rather than later?
- Is it ethical to refuse or delay infertility treatments in morbidly obese individuals pending weight reduction?

SUMMARY

Obesity is epidemic in the developed world and poses a well-established roadblock to successful parenthood. Obesity in one or both partners prolongs the interval to successful conception and increases costs and risks of infertility care. Once pregnancy is achieved, obesity is a major risk factor for pregnancy-related complications. Lifestyle modification remains central to treatment for all individuals, but, in the end, it may not have a substantive effect on the need for intervention by the infertility specialist unless the weight loss is substantial. Fortunately, pharmacologic and bariatric surgical options have given prospective parents new tools to achieve critical weight loss. The decision to proceed with infertility treatment versus waiting for meaningful weight reduction by medical or surgical options should be individualized and explored via shared decision making between patient and physician. Future research should focus on establishing best practices through high-quality clinical trials.

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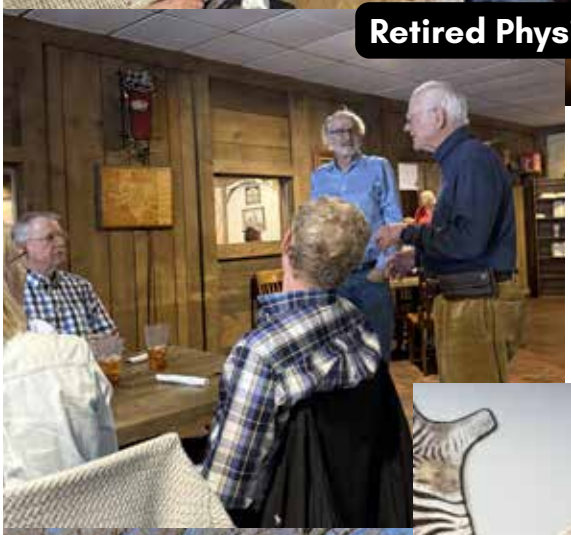

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