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REVIEW

Clinical Assessment of People With Obesity: Focus on Adiposity-Related Multimorbidity

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Abstract

Obesity is a chronic complex disease with deleterious effects on multiple organs and systems through a process called *lipotoxicity*. Obesity is commonly associated with a range of systemic comorbidities, including cardiovascular diseases, obstructive sleep apnea, type 2 diabetes mellitus, dyslipidemia, osteoarthritis, and depression. Unfortunately, these conditions can be overlooked in the clinical setting, yet early detection and intervention of obesity-related comorbidities can lead to significantly improved health outcomes and well-being. An important consideration for clinicians is that obesity is the root cause and its associated comorbidities are downstream conditions. This perspective may help prioritize the management of obesity in the clinical setting. Adopting this clinical approach to treating obesity may help to improve or resolve several related conditions simultaneously rather than treating each condition as an isolated unassociated disease. This comprehensive review is based on the published literature on PubMed and Google Scholar and summarizes the latest recommendations and guidelines from international associations when diagnosing multimorbidity associated with adiposity and can be a valuable resource for diagnosing and managing obesity in the primary care setting.

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The worldwide prevalence of obesity has more than doubled since 1990,[1] leading to an increased number of patients experiencing weight-related health problems. The prevalence of multimorbidity has emerged as a critical challenge within the health care field.[2] As a chronic, complex, and heterogeneous condition, obesity significantly complicates the management of multiple chronic diseases, necessitating a holistic approach from clinicians. Despite the growing recognition of this interrelationship, there is still a notable lack of comprehensive guidelines for addressing obesity in clinical practice.

Obesity serves as a root cause for a myriad of downstream health conditions.[3] The far-reaching impact of obesity on multiple organs and systems through lipotoxicity underscores its role as a central player in the development and progression of various comorbidities.[4] An example of this interconnectedness is evident in the cardiovascular-kidney-metabolic syndrome, which encompasses the intricate relationships between obesity, type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and cardiovascular disease (CVD).[5] Recognizing obesity not merely as an isolated condition but as a pivotal factor influencing a spectrum of other health issues has the potential to yield significant benefits across the management of a range of related health conditions.

This aim of this narrative review is to explore obesity-related multimorbidity within the clinical setting, analyzing current clinical approaches and the impact of obesity treatment on coexisting conditions. Furthermore, we propose strategies for integrated care with the ultimate goal of providing

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ARTICLE HIGHLIGHTS

- The increasing prevalence of obesity and its associated comorbidities presents a significant challenge in health care.
- Primary care physicians must recognize obesity-associated comorbidities to better provide holistic care.
- Treating obesity as a root cause is essential for improving the management of obesity-related comorbidities.

insights into more effective, holistic management practices that can enhance overall patient outcomes in the primary care setting.

METHODS

A comprehensive search was conducted in PubMed and Google Scholar from each database's inception to August 2024, limited to the English language. The search terms used were *obesity and multimorbidity*, *treatment*, *cardiorespiratory fitness*, *cardiovascular disease*, *respiratory disease*, *gastrointestinal disease*, *renal disease*, *endocrine disease*, *musculoskeletal disease*, and *mental disease*.

OBESITY DIAGNOSIS

Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) is a helpful screening tool for obesity (BMI $\geq$30 kg/m^2) in the clinical setting but is limited in differentiating between body fat, lean mass, and central vs peripheral fat deposition.[6] These limitations are particularly pronounced in individuals with intermediate BMI ranges, in men, and in elderly people, in whom BMI has poor sensitivity (42%) and high specificity (97%) in detecting obesity.[7] Furthermore, BMI cutoff values should be adjusted for ethnic-specific variations because body fat distribution varies among different populations.[8] Consequently, it is essential to incorporate additional measures such as waist circumference (WC) and waist-to-hip ratio (WHR) to assess fat distribution in clinical practice more accurately.[9]

A new adiposity index, the weight-adjusted waist index, offers a more nuanced approach to assessing cardiometabolic risk. This index, calculated by dividing WC by the square root of body weight, has a positive linear association with cardiometabolic morbidity and mortality.[10]

Bioimpedance analysis (BIA) is a widely used and cost-effective method for assessing body composition in clinical settings. The TANITA BIA system offers a valid measurement of percentage body fat in older adults.[11] However, it has some limitations, including an underestimation of body fat percentage compared with dual-energy x-ray absorptiometry (DEXA).[12] Additionally, its accuracy decreases as obesity increases,[13] and it relies on fixed hydration assumptions.[14]

Other nonanthropometric measures, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, DEXA, and air displacement plethysmography offer the capability to quantify body composition with high precision.[15] However, these methods are often cumbersome or costly to implement in the clinical setting, presenting significant barriers to their routine use.

A *Lancet* Commission recently proposed a new classification system for obesity, distinguishing between "clinical obesity" (patients with adiposity-related comorbidities) and "preclinical obesity" (patients with an increased BMI without associated comorbidities). The group also proposed using alternative methods to confirm excess adiposity, such as anthropometric measurements (eg, WC, WHR) or direct body fat measurement (eg, BIA, DEXA).[16]

CARDIOVASCULAR DISEASES

Hypertension

Obesity accounts for 65% to 78% of cases of primary hypertension (HTN).[17] Proper blood pressure (BP) measurements are crucial to diagnose HTN correctly. Using an improperly sized cuff bladder that does not appropriately surround the upper arm can lead to falsely elevated BP readings (Table 1).[18] Depending on the reference guidelines, there are different BP cutoff values to diagnose HTN.[19,20]

If HTN is suspected, it should be confirmed by repeated office BP

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TABLE 1. Cuff Bladder Sizes

Upper arm circumference (cm)	Cuff size (cm)
27-34	13 × 30
35-44	16 × 38
45-52	20 × 42

measurements over several visits or by out-of-office BP measurements using 24-hour ambulatory BP monitoring or home BP monitoring. This approach can detect white-coat or masked HTN.[19]

Treatment options include nonpharmacological approaches (Table 2).[19,21-26] Encouraging a more active lifestyle is crucial, especially for highly sedentary and deconditioned patients. The key is to "sit less, walk more, and exercise." When performing resistance training, caution should be taken, including avoiding heavy weights that could cause a Valsalva response, leading to a sudden increase in BP, a decrease in venous return, and potential complications such as arrhythmias or fainting.

There are no specific pharmacological recommendations for people with HTN and obesity that differ from nonobese hypertensive persons. Once HTN is confirmed, a BP target of less than 130/80 mm Hg is recommended for most patients[18-20] When selecting the best BP agent for people with obesity, it is necessary to consider coexisting metabolic syndrome. Thiazide diuretics and β-blockers (first and second generation) may raise blood glucose levels and convert insulin resistance to T2DM. Calcium channel blockers appear to be neutral,[27-29] whereas angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have a better metabolic profile and are preferred as initial therapy.[30]

Patients with obesity are prone to development of resistant HTN.[31] This tendency could be due to factors such as obstructive sleep apnea (OSA), volume expansion, inappropriately high plasma aldosterone concentrations, and sympathetic activation.[18] Spironolactone is one of the most effective add-on drugs for the treatment of resistant HTN,[32] whereas in patients with advanced CKD who are not undergoing dialysis, loop diuretics and chlorthalidone are the preferred options.[19]

Heart Failure

Long-term obesity is an independent risk factor for heart failure (HF) with preserved ejection fraction (HFpEF), whereas the connection between obesity and HF with reduced ejection fraction is less clear.[33] Data from the Framingham study revealed that for each increment of 1 unit in BMI, the risk of HF increases by 5% for men and 7% for women.[34]

Diagnosing patients with obesity and HFpEF may be challenging, especially if they are euvolemic and have unexplained dyspnea on exertion.[35,36] Typical symptoms such as fatigue, breathlessness, and ankle swelling can be mistaken for physical deconditioning and a sedentary lifestyle.[37] Also, due to the gradual onset of symptoms, clinicians should not wait for the patient to report shortness of breath or fatigue but should proactively screen for these symptoms to diagnose HFpEF sooner and refer the patient to a specialist.[38]

The initial evaluation for patients with suspected HF should include 12-lead electrocardiography (ECG), chest radiography, and basic investigations such as serum urea and electrolytes, creatinine, full blood cell count, and liver and thyroid function tests.[37] Transthoracic echocardiography plays a pivotal role in evaluating the diagnosis of HFpEF and uncovers other causes of dyspnea, including HF with reduced ejection fraction, valvular heart disease, and pulmonary HTN.[35,39]

Measurements of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are often used to help evaluate the presence and severity of HF.[40] However, in people with obesity, BNP and NT-proBNP cannot be used to rule out HFpEF, even when normal, because the renal disease can elevate natriuretic peptide concentration and obesity may lower it, reducing diagnostic sensitivity.[41,42]

The criteron standard for diagnosing HFpEF is invasive hemodynamic exercise

TABLE 2. Nonpharmacological Interventions for the Treatment of Hypertension

Intervention	Goal or Mechanism	Impact on hypertension
Weight loss	5% Reduction in body weight or more	↓ 3 mm Hg SBP and ↓ 2 mm Hg DBP
Diet	1200-1500 kcal for women and 1500-1800 kcal for men	
	Dietary approaches to stop hypertension (DASH)	↓ 7.62 mm Hg SBP and ↓ 4.22 mm Hg DBP
	DASH diet + behavioral weight management	BP: ↓11.7%
Reduce sodium intake	Less than 2300 mg/d or 1 tsp of table salt	Every 100 mmol of sodium restriction: ↓ 7.7 mm Hg SBP and ↓ 3.0 mm Hg DBP
Increase potassium consumption	Through dietary modification 3500 mg/d, except in CKD	↓ 4-5 mm Hg SBP
Reduce alcohol intake	Close to abstinence	↓ 3.3 mm Hg SBP and ↓ 2 mm Hg DBP
Daily physical activity and regular exercise	Aerobic exercise of moderate intensity: 150-300 min/wk **OR** Aerobic exercise of vigorous intensity: 75-150 min/wk Consulting with physical medicine professionals can help tailor exercise recommendations, improving compliance and preventing complications resulting from exercise	↓ 5-8 mm Hg SBP
Smoking cessation	Combining behavioral support with pharmacotherapy	Decreases daytime BP variability
Behavior therapy	Self-monitoring food intake, physical activity, and weight	Facilitates adherence to diet and activity recommendations

BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; ↓, Decrease.

testing.[35] Because this procedure has a greater cost, to enhance medical decision making regarding the need for invasive testing, clinicians can estimate the pretest probability of HFpEF using the H_2FPEF score with a score range from 0 to 9,[43] in which the presence of obesity is worth 2 points, pointing to the importance of adiposity in HFpEF.[43] Treating patients with obesity and HFpEF should include healthy lifestyle interventions because weight loss induced by caloric restriction or aerobic exercise training improves exercise capacity, and the combination of both may be additive.[44]

More recently, the STEP-HFpEF (Semaglutide Treatment Effect in People with Obesity and HFpEF) and STEP-HFpEF DM (Semaglutide Treatment Effect in People with obesity and HFpEF and type 2 diabetes) trials reported that glucagon-like peptide-1 receptor agonist (GLP-1RA) reduces HF symptom severity, improves exercise function, decreases inflammation, and reduces the risk for HF hospitalization.[45] Importantly, the magnitude of the benefit was directly correlated with the extent of weight loss.[46]

Sodium-glucose transport protein 2 inhibitors (SGLT2i), including empagliflozin and dapagliflozin, are indicated for all patients with HF in the absence of contraindications, even in the absence of T2DM and regardless of ejection fraction, to reduce HF hospitalizations and cardiovascular mortality and improve quality of life.[47] In addition, loop diuretics are recommended in patients with congestion to alleviate symptoms and signs.[37]

Coronary Artery Disease

Obesity increases the risk of coronary artery disease (CAD) by worsening the traditional cardiovascular risk factors[48] and is a main independent risk factor for coronary epicardial and microvascular endothelial dysfunction.[49] The Framingham Study found that each standard deviation increment in relative weight was associated with a 15% increase in the risk of cardiovascular events in men and 22% in women.[48] Diagnosing angina in patients with obesity can be challenging, with shortness of breath being a common symptom that may be the result of noncardiac causes including deconditioning and pulmonary disease. Thus, it is crucial to obtain a thorough clinical history to diagnose angina, in which shortness of breath may be the only symptom of CAD.[50]

The first line of testing for CAD in the general population includes standard laboratory biochemical blood testing, resting ECG, possible ambulatory ECG monitoring, resting echocardiography, and chest radiography for patients with atypical presentations, HF, or suspicion of pulmonary disease. The pretest probability and clinical likelihood of CAD should be evaluated to determine whether to pursue invasive or noninvasive ischemic testing.[50] In patients in whom CAD cannot be excluded by clinical assessment alone, either functional noninvasive testing (stress echocardiography, stress cardiac MRI, single-photon emission CT, positron emission tomography, myocardial contrast echocardiography, or contrast cardiac MRI) or anatomic noninvasive testing with coronary CT angiography (CTA) are recommended as the initial test for CAD in symptomatic patients with low to intermediate pretest probability.[50] Exercise ECG may be considered an alternative when no other imaging methods are available. It also complements the assessment of symptoms, exercise tolerance, arrhythmias, BP response, and event risk.[50]

Diagnostic tests for CAD may have limitations regarding obesity because excess weight can affect their accuracy and performance. For instance, ECG may be impacted by obesity by causing heart displacement, which results from the diaphragm being elevated in the supine position. Furthermore, increased cardiac workload and associated cardiac hypertrophy, as well as a widening distance between the heart and the recording electrodes may limit the sensitivity and specificity of ECG to detect ischemia. Other limitations include the accommodation of obese patients during CTA scans due to the weight limits of the table and gantry diameter. Additionally, image

quality for CTA, echocardiography, and nuclear scans can deteriorate with an increase in BMI, which is usually more challenging for people with a BMI above 40 kg/m^2.[26]

Lifestyle modifications and risk factor control, along with pharmacological treatment, are the cornerstone of treating patients with chronic CAD.[50] Exercise-based cardiac rehabilitation reduces cardiovascular mortality and hospitalizations and improves the quality of life.[51] Therefore, it is necessary to encourage participation in these programs that assess multiple patient comorbidities, focusing on an integrated approach.

More recently, in the SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) trial, semaglutide was found to be the first drug in its class to reduce by 20% the risk of major adverse cardiovascular events in obese patients with CVD without diabetes.[52] It may be speculated that the improvement was due at least in part to the beneficial effect of this class of drugs on microcirculation.[52] Other trials are currently under way studying the cardiovascular benefits of other GLP-1RA and dual agonists and major adverse cardiovascular event outcomes in obese patients without diabetes.

Atrial Fibrillation

The risk of atrial fibrillation (AF) increases by 28% per 5-unit increment in BMI, with a stronger association at higher BMI levels. Similarly, there is a 32% increased risk for AF per 10-cm increase in WC.[53] Obesity contributes to the predisposition and perpetuation of AF by various factors, such as direct and indirect effects of pericardial and epicardial fat,[54] shortened effective refractory period in the left atrium, slowed conduction in the pulmonary vein ostia, elevated LA filling pressure, left ventricular diastolic dysfunction, impaired left atrium stretching and contraction, and enlarged LA volume.[55] Obesity also contributes to the development of OSA, HTN, and T2DM, which independently increase AF risk.[54]

According to the US Preventive Services Task Force, there is insufficient evidence to evaluate the benefits and risks of screening for AF in asymptomatic adults aged 50 years and older, including those with obesity. In these recommendations, the decision to screen for AF is left to the clinician's discretion,[56] whereas the 2020 European Society of Cardiology guideline recommends screening patients older than 65 years.[57]

In addition to the standard physical examination, we suggest performing standard 12-lead ECG or a single-lead ECG tracing of 30 seconds[57] for screening patients aged 50 years or older with obesity and/or at least one risk factor for AF and to have a high level of suspicion in patients with obesity who are experiencing palpitations or are alerted by their monitoring devices of potential AF.

Weight loss and lifestyle management can significantly improve AF outcomes. In the LEGACY (*Long-term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort*) study, a weight loss of at least 10% resulted in a 6-fold greater probability of arrhythmia-free survival.[58] Similarly, in the ARREST-AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation) cohort study, aggressive risk factor reduction improved the long-term success of AF ablation.[59] The effect of pharmacologically induced weight loss on AF burden has not been documented.

The American Heart Association recommends 4 pillars for AF management: lifestyle and risk factor management, anticoagulation, rate control, and rhythm control.[54,60]

Other CVDs

Obesity is associated with a prothrombotic state,[61] low-grade inflammation, and impaired venous return secondary to increased intra-abdominal pressure.[62] Multiple studies have found that obesity significantly increases the risk of venous thromboembolism and pulmonary embolism.[62] The association between obesity and carotid artery disease is not entirely clear. Still, some studies have reported an association with WHR[63] and WC.[64]

The direct influence of obesity on the development of abdominal aortic aneurysm

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(AAA) is still unclear. A study found that abdominal adiposity was significantly associated with a 30% higher risk of AAA, and that risk increased by 15% per 5-cm increment of WC up to 100 cm for men and 88 cm for women.[65] Moreover, Wang et al[66] reported a significant 6% higher risk of AAA with each unit increase in baseline BMI. Another study found that after 12 weeks of weight loss, there was a significant difference in the diameter of the thoracic and abdominal aorta, especially in the group who lost 11.3%±0.6% of their weight.[67]

In summary, when evaluating a patient with obesity, it is important to inquire about symptoms such as chest pain, fatigue, shortness of breath, and palpitations. Patients may misinterpret these symptoms as being related to age, lack of fitness, or their obesity. Based on their responses, clinicians should proceed with the appropriate complementary studies mentioned previously.

RESPIRATORY DISEASES

Asthma

Obesity is strongly associated with asthma, and there may be a bidirectional relationship between the two. Obesity-driven systemic inflammation[68] can lead to worse asthma control, higher symptom burden, higher consumption of asthma medication, and reduced lung function when they are compared to their leaner counterparts.[69,70] The risk for development of asthma increases significantly with BMI, with an almost 250% increase among those with a BMI of 50 kg/m^2 or higher.[71]

Obesity can worsen lung mechanics in patients with preexisting asthma. However, people with severe asthma may become less active and deconditioned, which can lead to weight gain. Furthermore, increased oral corticosteroid usage can further aggravate the weight gain cycle.[68] There is a specific asthma phenotype called *asthma with obesity*, which is defined as individuals with obesity who have prominent respiratory symptoms and a different pattern of airway inflammation with little eosinophilic inflammation and low concentration of exhaled nitric oxide.[72]

It is crucial to confirm the diagnosis with objective measures before starting treatment because respiratory symptoms associated with obesity can mimic asthma. Measuring forced expiratory volume in 1 second from spirometry is recommended to document the variable expiratory airflow limitation.[72]

Regarding asthma management in people with obesity, in addition to inhaled corticosteroids the response to which may be attenuated, multimorbidity should be addressed, and weight reduction should be included in the treatment plan for better asthma control.[72] A recent study found that a 5% reduction in body weight significantly improves asthma control scores.[73] Furthermore, patients undergoing bariatric surgical procedures had significantly improved asthma control and quality-of-life scores after 12 months, irrespective of IgE levels.[74] Moreover, within a year or 2 after a bariatric operation, the risk of emergency department visits or hospitalization for asthma exacerbation decreases by 50%.[75]

It has been suggested that GLP-1RA could be a potential new treatment for asthma in individuals with obesity and T2DM due to its anti-inflammatory effects. A meta-analysis found that the use of light-molecular-weight GLP-1RA (exenatide, liraglutide, lixisenatide, and semaglutide) might be linked to a lower incidence of asthma in patients with these comorbidities.[76]

Obstructive Sleep Apnea

Obesity is one of the major risk factors for OSA. A 10% increase in body weight increases by 32% the risk for development of OSA,[77] which is diagnosed in up to 77% of patients considered for bariatric operation.[78]

Because OSA is associated with other disorders such as CVD and metabolic dysfunction, and treatment of OSA could potentially positively impact those comorbidities, recognition and diagnosis are key.[79,80] Breathing pauses of OSA cause sleep interruption and excessive daytime somnolence and may favor the adoption of a sedentary lifestyle, creating a vicious cycle.

It is unclear who should undergo screening for OSA[56]; however, people with obesity are at a higher risk for development of OSA. The American Academy of Sleep Medicine recommends screening individuals who are at high risk, such as those with HF, elevated BP, AF, resistant HTN, T2DM, stroke, BMI of 30 kg/m^2 or higher, and those who are preparing for bariatric surgical procedures. A validated questionnaire should be used for screening,[81] and the STOP-Bang questionnaire has reasonable sensitivity and specificity.[82] Those with a positive screen result should undergo polysomnography or home sleep apnea testing. Polysomnography is preferred over home sleep apnea testing in patients with advanced cardiorespiratory disease, neuromuscular weakness, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke, or severe insomnia.[79] Management of OSA involves improving daytime sleepiness through positive airway pressure (PAP) therapy, which includes continuous PAP (CPAP), auto-adjusting PAP, and bilevel PAP.[83]

Weight loss can improve OSA severity and cardiometabolic abnormalities, promoting overall health.[84] A 10% weight loss can reduce the apnea-hypopnea index by 26%.[85]

The SURMOUNT-OSA (*Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity*) trial findings suggest that tirzepatide could be a promising treatment for individuals with moderate to severe OSA and obesity, resulting in a 59% reduction in the baseline apnea-hypopnea index.[86] Similar results were reported for liraglutide 3.0 mg.[87]

ENDOCRINE DISEASES

Type 2 Diabetes Mellitus

Abdominal or visceral obesity is a major risk factor for development of T2DM.[88] Their coexistence is commonly referred to as "diabesity" due to the strong relationship they have.[89]

The US Preventive Services Task Force recommends screening for prediabetes and T2DM in adults aged 35 to 70 years who have overweight or obesity,[90] while the American Diabetes Association recommends testing in all adults of any age with overweight/obesity.[91] Prediabetes and T2DM can be diagnosed by fasting plasma glucose (FPG) value, glycosylated hemoglobin (HbA_{1c}) level, or oral glucose tolerance test.[91]

The American Association of Clinical Endocrinologists and the American College of Endocrinology recommend an HbA_{1c} target of 6.5% or lower for most patients with T2DM. This goal should be achieved without adverse outcomes such as hypoglycemia. In that case, individualization of glycemic goals is needed, and values of greater than 6.5% and 8% are accepted.[92] The European Society of Cardiology and European Association for the Study of Diabetes recommend an HbA_{1c} level of less than 7% to reduce microvascular complications.[93]

Weight management is crucial in improving glycemia and cardiovascular risk factors. The American Diabetes Association recommends maintaining a 5% or greater weight loss and achieving a 500 to 750 kcal/d energy deficit.[94] Moreover, sustained weight loss of greater than 10% may remit T2DM and decrease cardiovascular mortality.[94]

Regarding pharmacological treatment for T2DM, it is important to consider the impact on weight of the many therapeutic options available. Agents associated with weight loss, such as α-glucosidase inhibitors, SGLT2i, GLP-1RA, dual glucagon-like peptide 1/glucose-dependent insulinotropic polypeptide receptor agonist (tirzepatide), and amylin mimetics should be prioritized when possible. Metformin and dipeptidyl peptidase 4 inhibitors are a weight-neutral option.[94] Insulin and insulin secretagogues are associated with weight gain, and when necessary, patients should be counseled on mitigating strategies.

Metformin is still considered a first-line agent for treating T2DM in patients with HbA_{1c} levels of less than 7.5%. However, if the patient has an HbA_{1c} level of 7.5% or greater and/or established or high atherosclerotic cardiovascular disease (ASCVD) risk and/or CKD, initiation of SGLT2i or GLP-

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1RA is recommended. Therapy must be evaluated every 3 months until targets are achieved.[92,93]

Hypothyroidism

Hypothyroidism in people with obesity can hinder weight loss and worsen related health conditions. Recent research has revealed that the prevalence of overt hypothyroidism in this population is around 14%, whereas subclinical hypothyroidism affects 14.6% of patients.[95] According to the European Society of Endocrinology, all patients with obesity, particularly those with severe obesity who are considering bariatric operations, should be tested for thyroid function.[89]

The primary test for screening hypothyroidism is serum thyrotropin (TSH). If TSH levels are abnormal, follow-up should include measurements of free thyroxine (T_4) levels, and the European Society of Endocrinology suggests adding measurement of thyroid peroxidase antibodies.[89,96] When treating hypothyroidism, T_4 replacement therapy is the recommended course of action.[97] Total body weight is typically used to calculate T_4 dosage.[97] However, estimating lean body mass may be more helpful in determining dosage and shortening the time to attain a stable dose.[98]

Gastrointestinal disorders such as *Helicobacter pylori*—related gastritis, atrophic gastritis, or celiac disease should also be evaluated in patients with unexpectedly higher dose requirements. Dose adjustments should be made after changes in body weight and follow-up with TSH after 4 to 6 weeks of any dosage change.[97]

Dyslipidemia

Dyslipidemia is present in 62% to 68% of individuals with obesity and 53% to 62% of people with overweight.[99] According to the American Association of Clinical Endocrinologists and the American College of Endocrinology, patients with overweight or obesity should have their lipid levels checked through a comprehensive lipid panel that includes triglycerides, high-density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C), total cholesterol, and non—HDL-C.[77] To manage dyslipidemia, it is important to identify the presence of metabolic syndrome and to determine the 10-year ASCVD risk using the pooled cohort equations.[100] For patients with an endocrine disorder, an ASCVD risk between 5% and 19.9% and additional risk-enhancing factors in which the decision to start statin therapy remains uncertain, measuring coronary artery calcium (CAC) for assessment of subclinical atherosclerosis may be necessary.[100]

If the patient does not have T2DM or ASCVD but has an LDL-C level greater than 70 mg/dL (to convert LDL-C value to mmol/L, multiple by 0.0259) and a 10-year ASCVD risk greater than 7.5%, or ASCVD risk from 5% to 7.4% plus one or more risk-enhancing factors, or CAC score over the 75th percentile for age, sex, and race, or CAC score greater than 100, it is advised to start pharmacological treatment.[100]

Besides healthy lifestyle interventions, treatment with statins is the cornerstone of dyslipidemia therapy.[101] However, some high-intensity statins, like rosuvastatin and atorvastatin, may negatively impact glucose metabolism, causing modest blood glucose elevations.[102-104] Although statins can affect glycemic profile, their cardiovascular benefits outweigh the risk of new-onset T2DM.[105] A safe and beneficial statin in people with metabolic syndrome could be pravastatin or pitavastatin.[106,107]

Nonstatin therapy can be added for additional LDL-C lowering. Ezetimibe will decrease LDL-C by 13% to 20%, bile acid sequestrants by 15% to 30%, proprotein convertase subtilisin/kexin type 9 inhibitors by 43% to 64%, and bempedoic acid by 24% when given alone, 18% with concomitant statin therapy, and 38% to 40% with ezetimibe.[101,108] Lipid profiles should be updated and a new cardiovascular risk assessment should be performed after the patient loses 5% of body weight.[101] Losing 5 kg to 8 kg of weight can reduce LDL-C levels by approximately 5 mg/dL and increase HDL-C levels by 2 to 3 mg/dL (to convert HDL-C value to mmol/L, multiple by 0.0259).[109]

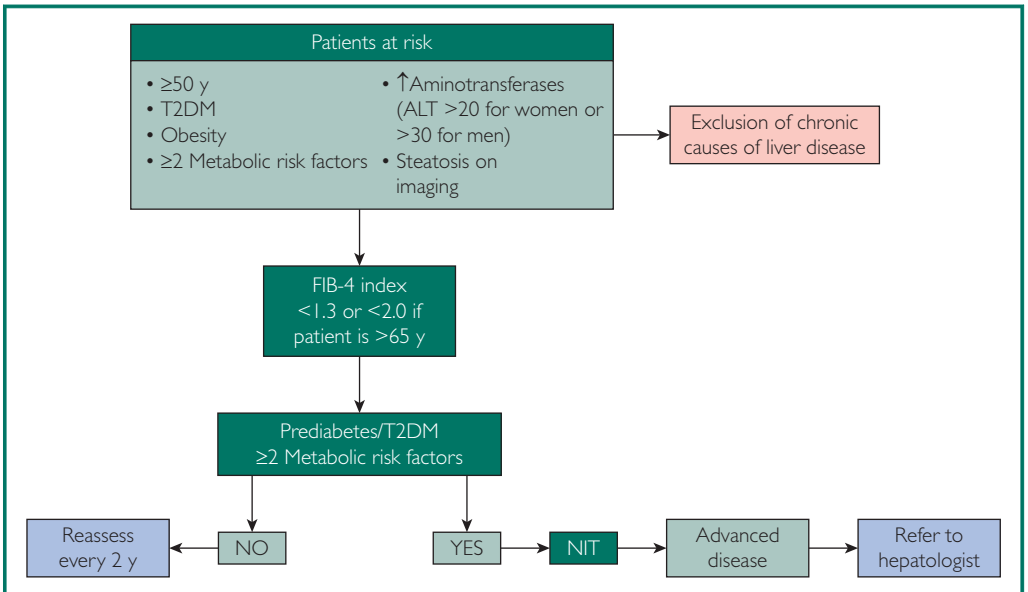

FIGURE 1. Clinical assessment of metabolic dysfunction–associated steatotic liver disease. ALT, alanine aminotransferase; FIB-4, fibrosis 4 index; NIT, noninvasive test; T2DM, type 2 diabetes mellitus.

Other Endocrine Diseases

If a patient with central obesity has uncontrolled HTN and/or T2DM, it is important to rule out Cushing syndrome. This determination is especially crucial if the patient is a candidate for bariatric surgical treatment because hypercortisolism can complicate the outcomes. The recommended screening method is 1-mg late-night dexamethasone suppression.[89]

Polycystic ovary syndrome is associated with insulin resistance and can be worsened by obesity.[110,111] It should be suspected in women with symptoms of hyperandrogenism, chronic anovulation, and polycystic ovaries on ultrasonography.[112,113] The initial work-up should include measuring calculated free testosterone, free androgen index, or calculated bioavailable testosterone serum total testosterone and serum 17-hydroxyprogesterone.[113,114]

In men with moderate/severe obesity, the prevalence of hypogonadism was found to be 45%.[115] Symptoms like erectile dysfunction, weakness of morning erections, reduced sexual desire, muscle weakness, gynoid fat distribution, hot flashes, osteoporosis, infertility, changes in mood, fatigue, and sleep disturbances should be assessed. If clinical features are present, total and free testosterone should be measured or calculated with sex hormone–binding globulin and albumin concentrations.[89]

GASTROINTESTINAL TRACT DISORDERS

Metabolic Dysfunction–Associated Steatotic Liver Disease

Obesity is significantly associated with a 3.5-fold increased risk for development of metabolic dysfunction–associated steatotic liver disease (MASLD) when compared with those with normal weight.[116] The risk further increases by 20% with every 1-unit increase in BMI.[116]

One of the challenges in MASLD is early detection because most patients are asymptomatic (Figure 1). The European Association for the Study of the Liver/European Association for the Study of Diabetes and European Association for the Study of Obesity recommend screening at-risk patients, which includes those older than 50 years, with T2DM, or with components of metabolic syndrome.[117] The initial evaluation should include medical history, alcohol

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intake, and routine laboratory tests with the assessment of liver enzymes.[118] For patients with abnormal results on liver function tests and cardiometabolic risk factors, liver imaging is recommended to detect steatosis because the updated diagnostic criteria for MASLD are based on the presence of hepatic steatosis on imaging or biopsy and the finding of any cardiometabolic risk factor.[119] It is important to note that ultrasonography is only accurate in detecting steatosis when the total area exceeds 20% of the liver area and has suboptimal sensitivity for lesser degrees of steatosis.[118] Additional testing should be used to rule out etiologies such as alcoholic liver disease, hemochromatosis, autoimmune disease, or viral hepatitis.[120] The American Gastroenterological Association recommends testing for advanced hepatic fibrosis using the fibrosis 4 index. For patients with a low risk of fibrosis but who have T2DM and/or more than 2 metabolic risk factors, a second noninvasive test such as an enhanced liver fibrosis blood test, vibration-controlled elastography, or magnetic resonance elastography is recommended.[121] Given the risk of indolent progression to more severe liver disease, particularly in obese individuals, primary care practitioners should maintain a high index of suspicion for MASLD.

Treatment of MASLD focuses primarily on weight reduction, lifestyle modifications, and management of comorbidities.[118] Weight loss of 5% of total body weight can decrease hepatic steatosis, 7% can resolve steatohepatitis, and up to 10% can limit ongoing inflammatory processes that contribute to the progression of MASLD.[122]

Regarding pharmacotherapy, incretins such as semaglutide may significantly improve transaminase levels and MASLD scores, with recent studies reporting that they may be effective in reducing liver fibrosis.[123-125] Pioglitazone has been found to improve liver histology, primarily steatohepatitis, in patients with MASLD irrespective of the presence of T2DM.[126] A new medication, resmetirom, has received provisional approval by the US Food and Drug Administration for treating MASLD, although it does not exert weight loss.[127]

Bariatric surgical treatment appears to be effective at treating MASLD, with significant improvement in liver fibrosis.[128] It reduces steatosis by 66%, inflammation by 50%, ballooning degeneration by 76%, and fibrosis by 40%. Although bariatric operations can result in complete resolution of MASLD in patients with obesity, 12% of patients may experience new or worsened features of MASLD postoperatively.[129]

Gastroesophageal Reflux Disease

Obesity is a significant risk factor for gastroesophageal reflux disease (GERD), with 50% of individuals with obesity experiencing GERD symptoms.[130] Physiologic abnormalities, such as motility disorders detected by esophageal manometry, have been identified in people with a BMI greater than 35 kg/m^2. Other contributing factors include increased intra-abdominal pressure due to abdominal obesity and delayed gastric emptying caused by neurohumoral mechanisms. Central obesity has also been associated with complications of GERD, such as erosive esophagitis, Barrett esophagus, and esophageal adenocarcinoma.[130]

It is important to screen for classic reflux symptoms (heartburn and regurgitation) and extraesophageal symptoms such as chronic cough, asthma, laryngitis, and noncardiac chest pain. For patients without alarm symptoms (dysphagia, weight loss, and gastrointestinal tract bleeding), an initial 8-week trial of proton pump inhibitors is recommended.[131]

The decision to perform upper endoscopy in patients with obesity should be individualized, focusing on those with alarm symptoms, those with symptom recurrence after discontinuing proton pump inhibitors, or those who have multiple risk factors for Barrett esophagus (chronic GERD and 3 or more of the following risk factors: male sex, age greater than 50 years, White race, tobacco smoking, central adiposity, and history of Barrett esophagus or esophageal cancer in a first-degree relative).[132] Before upper endoscopy, it is important to consider whether the patient is using a GLP-1RA. The GLP-1RAs significantly increase the

risk of retained gastric contents, which can complicate endoscopic mucosal evaluation and airway protection. To mitigate this risk, a clear liquid diet for at least 24 hours before the procedure or withholding GLP-1RA is recommended.[133]

Management of GERD should include dietary and lifestyle modifications and, importantly, weight loss for overweight or obese individuals. Proton pump inhibitors should be taken 30 to 60 minutes before a meal for optimal symptom control. Although Roux-en-Y gastric bypass is primarily used for weight loss, it also offers the added benefit of improving acid reflux.[131]

Other Gastrointestinal Diseases

Obesity is a risk factor for gallstone formation[134] by altering lipid metabolism and increasing cholesterol secretion. Additionally, obesity is recognized as a significant risk factor for chronic pancreatitis, likely due to increased inflammation and intrapancreatic fat. One study found that patients with chronic pancreatitis had higher levels of visceral fat and pancreatic fat fraction compared with those without chronic pancreatitis.[135]

RENAL DISEASE: CHRONIC KIDNEY DISEASE

Obesity is a well-known independent risk factor for the development and progression of CKD.[136] There is a specific disease called *obesity-related glomerulopathy* (ORG), characterized by glomerulomegaly and focal and segmental glomerulosclerosis. Nonetheless, compared with primary focal and segmental glomerulosclerosis, a lower percentage of glomeruli is usually affected.[137]

The most common presentation of ORG is proteinuria and normal urinary sediment. However, up to one-third of patients may have development of proteinuria in the nephrotic range. Because of its indolent course, it can remain undetected until renal function is severely compromised.[137] Although there is no evidence to recommend screening for CKD in asymptomatic adults, it may be beneficial to consider screening in individuals with obesity.

It is crucial to accurately estimate renal function for proper staging, disease monitoring, and pharmacotherapy adjustments because calculations of glomerular filtration rate (GFR) based on weight, height, or body surface area may underestimate renal function.[138] The equation from the Chronic Kidney Disease Epidemiology Collaboration offers a good GFR prediction in patients with obesity and CKD with a GFR of 60 mL/min per 1.73 m^2 or less. Indexing measured GFR with body surface area using ideal body weight has less bias than measured GFR scaled with body surface area using real body weight.[139]

The albuminuria to proteinuria ratio may not be present in earlier stages. Therefore, a biomarker of ORG has been proposed, namely, the ectopic accumulation of lipids in the kidney or fatty kidney. It can be assessed through renal ultrasonography, ultrasonographic elastography, CT, and MRI.[137] Weight loss is recommended as the cornerstone of the treatment to reduce proteinuria and slow CKD progression. After bariatric operations, the risk of albuminuria or proteinuria decreases by 58% and 69%, respectively.[140] Another measure to control proteinuria is angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, which can also improve renal blood flow and reduce BP.[141] It is essential to manage the systolic BP target of less than 120 mm Hg using standardized office BP measurement.[142]

Sodium-glucose transport protein 2 inhibitor has been found to lower the risk of CKD progression or death from cardiovascular causes. In the EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) trial, empagliflozin reduced the risk by 28% among patients with and without T2DM.[143] In the FLOW (Evaluate Renal Function with Semaglutide Once Weekly) trial involving patients with T2DM and CKD, semaglutide had kidney protection effects. It significantly reduced the risk of major kidney disease events by 24% and reduced the risk of death from kidney-related or cardiovascular causes.[144]

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MUSCULOSKELETAL DISEASES: OSTEOARTHRITIS

The risk for development of knee osteoarthritis increases by 35% with every 5-unit increase in BMI.[145] Furthermore, women are more susceptible to this association than men.[146] Obesity is one of the most influential and modifiable factors in osteoarthritis, creating a cyclical effect. Osteoarthritis can limit people's mobility, making it difficult to lose weight and manage obesity-related comorbidities such as HTN and T2DM, worsening obesity. The forces on weight-bearing joints can be equivalent to 1.5 to 5 times the body weight, depending on the inclination of the walking surface and the activity performed. In addition, metabolically active mediators induced by obesity have been found to promote inflammatory responses in joint cartilage.[147]

Symptoms of osteoarthritis may be misidentified as a normal part of aging, which could delay a patient from seeking care from a health care professional.[148] Symptoms include pain while bearing weight and relief from rest, stiffness following inactivity, instability, and deformity leading to loss of function. Radiographs reveal osteophyte formation and narrowing of joint space.[149] The American College of Rheumatology strongly recommends any exercise based on patient preferences, accessibility, and affordability.[150] Supervised exercises are most effective. A weight loss of 5% or more is related to symptoms and functional improvement. For people with joint instability, walking difficulties, or pain, using a cane and tibiofemoral knee braces are strongly recommended.[150]

Pharmacological treatment includes topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs). However, NSAIDs, especially in people with obesity and metabolic syndrome, have an increased risk of CVD, HTN, worsening of kidney function, and adverse gastrointestinal tract effects. If the patient is taking acetylsalicylic acid (ASA) for cardioprotection, ibuprofen should not be given for pain management because it interferes with the capability of ASA to acetylate platelet COX-1 (cyclooxygenase 1) irreversibly. Conversely, combining ASA and coxib may enhance the protective effect in the gastric mucosa.[151]

Patients who cannot take or do not respond well to NSAIDs may benefit from intra-articular corticosteroids. The use of glucosamine and chondroitin, acupuncture, intra-articular hyaluronic acid injections, and platelet-rich plasma is controversial due to varying interpretations of the evidence.[150] A recent study revealed that semaglutide may offer benefits in pain management and joint function for individuals with obesity and knee osteoarthritis.[152]

Restoration of function is imperative because physical activity is a core component for weight control and the management of several obesity-related comorbidities.

MOOD DISORDERS: DEPRESSION

People with obesity have an increased risk for depression.[153] Obesity and depression are biologically linked by the dysregulation of the hypothalamic-pituitary-adrenal axis, which is associated with insulin resistance, increased blood cholesterol levels, and higher BP.[154] They are also behaviorally linked because people with depression tend to be sedentary and have unhealthy nutritional intake.[155,156] Moreover, depression is a risk factor for metabolic syndrome[157] and CVDs.[158] A meta-analysis revealed that people with depression have a significant 30% increased risk for CAD and myocardial infarction.[159] The presence of depression lowers the chances of weight loss, creating a vicious circle.[160]

The Patient Health Questionnaire-9 (PHQ-9) is the most used measure for screening symptoms of depression in the primary care setting.[161] However, clinicians must also evaluate contextual factors and general functioning rather than rely solely on questionnaires to assess for the presence of a mood disorder.[162]

There are several strategies for treating mood disorders, including nonpharmacological measures such as sleep hygiene, regular exercise, and having a healthy diet. Substance misuse should also be assessed, and

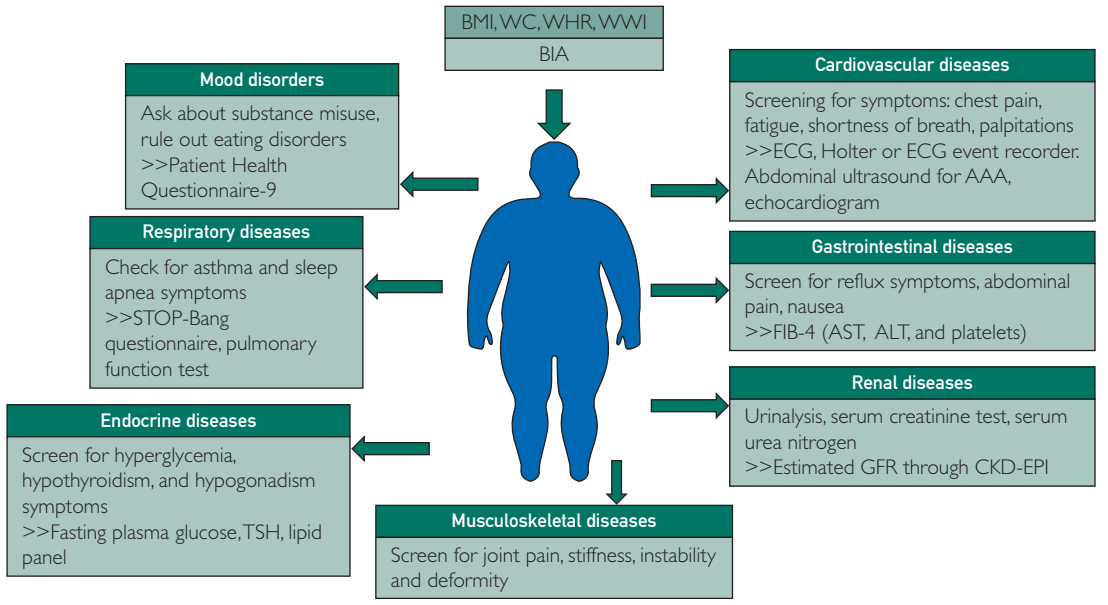

FIGURE 2. Initial assessment of patients with obesity in the clinical setting. AAA, abdominal aortic aneurysm; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIA, bioimpedance analysis; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECG, electrocardiogram; FIB-4, fibrosis-4; GFR, glomerular filtration rate; TSH, serum thyrotropin; WC, waist circumference; WHR, waist-to-hip ratio; WWI, weight-adjusted-waist index; >>, perform.

the patient should be referred to an addiction specialist when identified. Evidence-based psychotherapy, such as cognitive behavioral therapy, may suffice for mild cases of depression. However, moderate to severe cases should also be treated with medication[162] or with novel approaches, including repetitive transcranial magnetic stimulation.[163]

The American College of Physicians recommends starting with a second-generation antidepressant, such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.[164] Serotonin reuptake inhibitors are preferred for hypertensive patients because they do not increase BP. Atypical antipsychotics such as aripiprazole, olanzapine, and risperidone are effective as an adjunctive treatment for certain depressive disorders, but caution should be taken because they are associated with weight gain.[165]

OTHER DISEASES

Excess body weight is related to an increased risk of some malignant diseases. One study found that in men, a 5-kg/m^2 increase in BMI was significantly associated with esophageal adenocarcinoma and thyroid, colon, and renal cancers. In women, a significant association was found between a 5-kg/m^2 increase in BMI and endometrial and gallbladder cancers, esophageal adenocarcinoma, and renal cancers.[166]

Obesity is also linked to rheumatic diseases. A study found that a 1-SD increase in BMI significantly raises the incidence of rheumatoid arthritis, osteoarthritis, psoriatic arthropathy, gout, and inflammatory spondylitis. The effect is more pronounced in women for gout and psoriatic arthropathy.[167] Furthermore, obesity is associated with a 14% increased risk for development of psoriasis for each incremental unit of weight-adjusted waist index.[168]

CARDIORESPIRATORY FITNESS

In recent years, cardiorespiratory fitness (CRF) and physical activity have been identified as key factors in predicting CVD prognosis in people with and without obesity. An 11% reduction in all-cause mortality is

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TABLE 3. Multi-assessment of People With Obesity in the Clinical Setting

Obesity measurements		
Anthropometric measurement: BMI, waist circumference, waist-to-hip ratio, WWI Nonanthropometric measurement: BIA or DEXA for body composition. If available, cardiopulmonary exercise test to assess cardiorespiratory fitness		
Cardiovascular		**Treatment**
Hypertension	Repeated office blood pressure measurements with the correct cuff size, ABPM, when hypertension is suspected but could not be confirmed with regular sphyngobaumanometer Risk factors for resistant hypertension	Nonpharmacological therapies Pharmacological therapy: ACEIs or ARBs, CCBs
Heart failure with preserved ejection fraction	Screen for symptoms and signs of heart failure ECG, chest x-ray, NT-proBNP, BNP. Transthoracic echocardiography Calculate H_2FPEF score Refer to cardiology for patients with intermediate H_2FPEF score for which additional testing is needed	Lifestyle interventions and exercise training Manage comorbidities Pharmacological therapies: SGLT2i or GLP-1RA Loop diuretics if there are signs of congestion
Coronary artery disease	Look for symptoms of angina and atypical presentation Pretest probability ECG, laboratory testing, coronary calcium CT scan, stress testing if symptoms of coronary artery disease	Control risk factors Cardiac rehabilitation
Atrial fibrillation	Check pulse 12-Lead ECG, 24-h Holter; ECG event recorder, or use of gadgets (smartwatches or devices) meant to detect atrial fibrillation	Risk factor management Anticoagulation Rate control Rhythm control
Respiratory		
Asthma	Determine the symptoms of recurrent airway obstruction: wheezing, shortness of breath, chest tightness, and/or cough Assess asthma severity Evidence of variable expiratory airflow limitation: positive bronchodilator responsiveness test with spirometry CBC, chest x-ray	Inhaled corticosteroids Weight reduction
Obstructive sleep apnea	Identify high-risk patients Daytime sleepiness, habitual snoring, apnea during sleep, or hypertension Screening tool: STOP-Bang questionnaire Home-based polysomnography vs overnight pulmonary oximetry depending on clinical probability If the Stop-Bang score is ≥4, refer to sleep medicine for polysomnography or home sleep apnea testing	Weight loss Positive airway pressure therapy Tirzepatide, liraglutide
Endocrine		
T2DM	Screen patients every 3 y Fasting plasma glucose and/or HbA_{1c} Look for hyperglycemia symptoms	≥5%-10% Weight loss Start metformin Add SGLT2i, GLP-1RA, dual GLP-1/GIP receptor agonist, DPP4i, or thiazolidinedione according glycemic target Control every 3 mo

Continued on next page

TABLE 3. Continued

Endocrine		
Hypothyroidism	Test TSH	T_4 replacement therapy using lean body mass to calculate dosage
Hyperlipidemia	Assess lipid panel Calculate 10-y ASCVD risk	Weight reduction Statin therapy: pravastatin or pitavastatin Nonstatin therapy: ezetimibe, bile acid sequestrants, PCSK9 inhibitors
Other disorders	Cushing syndrome: screening in patients undergoing bariatric operations, central obesity with uncontrolled hypertension and/or T2DM. Test: overnight 1-mg dexamethasone suppression test PCOS: women with hyperandrogenism, ovulatory dysfunction, and polycystic ovaries on ultrasonography. Order calculated total and bioavailable testosterone, 17-hydroxyprogesterone Male hypogonadism: patients with severe obesity and erectile dysfunction, reduced sexual desire, muscle weakness, gynoid fat distribution, hot flushes, infertility, osteoporosis, changes in mood, fatigue, and sleep disturbances. Order total and bioavailable testosterone	
Gastrointestinal		
Metabolic dysfunction—associated steatotic liver disease	Screen with FIB-4 in patients with 2 or more metabolic risk factors every 1-2 y If FIB-4 score is >1.3, investigate fibrosis using elastography or ELF blood test (tissue inhibitor of metalloproteinase 1, aminoterminal propeptide of type III procollagen, and hyaluronic acid)	Risk assessment, referral to gastroenterology or hepatology Weight reduction ≥5%-10% and control risk factors Pharmacotherapy Bariatric operation
Gastroesophageal reflux disease	Screen for heartburn, regurgitation, and extraesophageal symptoms Start 8-wk PPI trial Evaluate upper endoscopy: alarm symptoms, risk factors for Barrett esophagus, and recurrence of symptoms after the PPI trial	Diet and lifestyle changes Weight loss PPI 30-60 min before meals
Other disorders		Check for symptoms of dyspepsia, biliary colic, and pancreatic insufficiency
Renal		
Obesity-related glomerulopathy	Check urinary sediment and proteinuria Calculate GFR through CKD-EPI Albuminuria Renal ultrasonography, CT, MRI to assess fatty kidney if abnormal GFR	Control of risk factors, weight loss Decrease proteinuria through ACEIs/ARBs for goal SBP <120 mm Hg SGLT2i, GLP-1RA
Musculoskeletal		
Osteoarthritis	Screen for symptoms such as knee, ankle or hip pain while bearing weight, stiffness following inactivity, instability, and deformity Knee x-ray with a standing posteroanterior view	Exercises, supervised exercises Weight loss of ≥5% NSAIDs or intra-articular corticosteroids Joint replacement
Mood disorder		
Depression	Screen depression with Patient Health Questionnaire-9 Evaluate substance misuse	Sleep hygiene, regular exercise, healthy diet Cognitive behavioral therapy Pharmacotherapy: SSRIs, atypical antipsychotics

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Cancer	
Increased risk	Men: esophageal adenocarcinoma, thyroid, colon, renal
	Women: endometrial, gallbladder, renal, esophageal adenocarcinoma

ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BIA, bioimpedance analysis; BMI, body mass index; BNP, B-type natriuretic peptide; CBC, complete blood cell count; CCB, calcium channel blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; DPP4i, dipeptidyl peptidase 4 inhibitor; ECG, electrocardiogram; ELF, enhanced liver fibrosis; FIB-4, fibrosis 4; GFR, glomerular filtration rate; GIP, gastric inhibitory polypeptide; GLP-1RA, glucagón-like peptide-1 receptor agonist; H_2FPEF, risk stratification tool for diagnosing heart failure with preserved ejection fraction; HbA_{1c}, glycosylated hemoglobin; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PCOS, polycystic ovary syndrome; PCSK9, proprotein convertase subtilisin/kexin type 9; PPI, proton pump inhibitor; SBP, systolic blood pressure; SGLT2i, sodium-glucose transport protein 2 inhibitor; SSRI, selective serotonin reuptake inhibitor; T_4, free thyroxine; T2DM, type 2 diabetes mellitus; TSH, thyrotropin; WWI, weight-adjusted waist index.

associated with each 1 metabolic equivalent increase in CRF,[169] regardless of sex or race.[170] Moreover, CRF has been linked to lower mortality from non-CVD, noncancer causes, including diabetes, kidney disease, chronic respiratory disease, acute respiratory and infectious disease, injuries, and other non-CVD noncancer-related conditions.[171] In different populations, CRF has been reported to be a more important predictor than body composition, and in some studies, CRF appears to attenuate mortality risk in patients with obesity who are fit.[172-174] Given the growing availability of commercial metabolic exercise testing units at competitive prices, the cardiopulmonary exercise test should be incorporated into health screenings to assess CRF.[175-177]

Figure 2 provides an overview of the initial assessment of the patient with obesity in the clinical setting.

Table 3 summarizes obesity-related comorbidities and their assessment.

OBESITY TREATMENT

The advances in managing obesity encompass several disciplines to achieve the best outcomes. A comprehensive discussion of these therapies is beyond the scope of this review. Primary care professionals can use the 5As counseling framework (Assess, Advise, Agree, Assist, and Arrange) to build and coordinate a multidisciplinary team to support patients in their weight management journey.[178]

Referrals to programs that offer intensive lifestyle interventions, pharmacotherapy, and/or metabolic/bariatric surgical intervention may be necessary. Pharmacotherapy and metabolic/bariatric operations produce greater and more sustained weight loss, which may be necessary to achieve a healthy outcome.[179,180] As medical professionals, our aim should be to recognize opportunities to help our patients improve their health by managing their weight. This could involve creating a safe space to start a conversation about weight management, addressing obesity-related comorbidities while recognizing their impact on weight, and potentially referring patients for advanced treatments. Obesity management continues to evolve as more effective therapies are developed and supported by robust randomized clinical trials and ongoing research into novel pharmacotherapeutic mechanisms. These developments are anticipated to transform the approach to obesity over the next decade.[181-186]

REAL WORLD CLINICAL CASES

Case 1

A 57-year-old man with a BMI of 37 kg/m^2 and no documented medical history of serious disorders comes to see his primary care clinician because of occasional palpitations lasting a few minutes every few weeks. He does not exercise much and feels hungry throughout the day, struggling to limit his caloric intake. He does not feel sleepy but does feel tired all day long. His most recent medical evaluation included a 24-hour Holter monitoring, which returned negative results. He was also found to have impaired FPG, low levels of HDL-C, and high triglyceride values. Further testing, which included an extended ECG event recording, overnight oximetry followed by polysomnography, and

additional blood tests, revealed paroxysmal AF, moderate to severe OSA, elevated high-sensitivity C-reactive protein, and liver enzymes. Liver ultrasonography identified significant steatosis.

Treatment with CPAP was initiated, and the patient received a formal exercise prescription along with a recommendation to sign up at a local fitness center. He was also referred to a dietitian and enrolled in a commercial weight loss program. Three months later, the patient had become increasingly more active, his tiredness had resolved, and his appetite had decreased, likely due to the treatment for OSA and increased physical activity. However, his weight had decreased only modestly, prompting the decision to initiate weekly subcutaneous tirzepatide injections. Six months later, the patient's BMI was 27 kg/m^2, his palpitations had resolved, and the requirements for CPAP had also decreased. Additionally, high-sensitivity C-reactive protein levels and liver enzyme levels had normalized.

Case 2

A 46-year-old woman with a BMI of 33 kg/m^2 and no cardiac history visits her primary care clinician because of worsening dyspnea on exertion. She is sedentary and reports joint discomfort, mainly in the knees. The patient is not motivated to start a diet or an exercise program. She feels tired all day and sits most of the time due to dyspnea on exertion and knee discomfort. Initial evaluation revealed no major abnormalities on physical examination or blood tests except hepatojugular reflex, impaired FPG level, and a TSH value of 8.0 mIU/L. Lipid, liver enzyme, and NT-proBNP levels and markers of inflammation were within normal limits. Following a comprehensive reevaluation by her clinician, including transthoracic echocardiography, pulmonary function test, and additional clinical screening tests, the patient was diagnosed with grade 3 diastolic dysfunction with normal left ventricular ejection fraction, mildly elevated pulmonary systolic pressure on echocardiography, and an obstructive pattern on pulmonary function testing with acetylcholine. She was also diagnosed with clinical depression.

After receiving appropriate treatment for hypothyroidism, HFpEF, bronchodilators, as-needed NSAIDs for osteoarthritis, and cognitive behavioral therapy for her depression, the patient was able to implement a tailored exercise program including resistance training, aerobic exercises, and elasticity training. As a result, she increased her physical activity by walking an average of 11,000 steps daily. Her mood and her functional capacity improved significantly. At that point the patient felt motivated to enroll in a commercial weight loss program, leading to substantial weight loss and achieving a current BMI of 26 kg/m^2.

Discussion of Cases

These cases illustrate real-world clinical scenarios in which patients with obesity underwent a thorough and multisystem evaluation, leading to the identification of several coexisting adiposity-related comorbidities. The cases reveal that when adiposity-related comorbidities are managed in conjunction, patients may improve in several domains at once, decreasing barriers to physical activity and other healthy behavioral changes.

CONCLUSION

Obesity is a chronic and preventable disease that negatively impacts health. It is often the root cause of many diseases and can worsen preexisting conditions. At the same time, through this complex interconnectivity, comorbidities can make obesity management more difficult.

Primary care clinicians play a crucial role in evaluating patients with obesity. However, the task can be challenging and often cannot be achieved alone. In this review, we provide a systematic overview of the diagnosis and management of common obesity-related disorders, aiming to equip health care professionals with the knowledge and tools necessary to improve therapeutic outcomes. They all represent opportunities to help our patients address the root cause of the threat to their health and weight. As more

obesity treatments are proven safe and increasingly effective, facilitating our patients' access to those treatments is crucial to protect health. Whether those treatments are started in the office setting or require a referral, patient awareness and engagement offer the best opportunity to improve/prevent the progression of obesity-related disorders.

POTENTIAL COMPETING INTERESTS

Dr Acosta has received grants or contracts from VIVUS Inc, Rhythm Pharmaceuticals, Inc, Regeneron Pharmaceuticals Inc, Boehringer Ingelheim, VIVUS Pharmaceuticals, and Novo Nordisk A/S (all paid to his institution), has received royalties or licenses from Phenomix Sciences (paid to his institution), has received consulting fees from Amgen Inc, RareStone Group, and Bausch Health Companies Inc (all 3 paid to his institution), Boehringer Ingelheim International GmbH, Regeneron Pharmaceuticals Inc, Currax Pharmaceuticals LLC, and Structure Therapeutics, Inc, has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from VIVUS Pharmaceuticals (paid to his institution), Lilly, and Boehringer Ingelheim International GmbH, has received support for attending meetings and/or travel from Currax Pharmaceuticals LLC (paid to his institution), has patents planned, issued, or pending related to nutrition and weight loss, has participated on a data safety monitoring board or advisory board for Amgen Inc, Boehringer Ingelheim International GmbH, Currax Pharmaceuticals LLC, Structure Therapeutics, Inc, and Regeneron Pharmaceuticals Inc (all paid to his institution), and has stock or stock options in Gila Therapeutics and Phenomix Sciences; Dr Borlaug has received consulting fees from Amgen Inc, ARIA CV Inc, Boehringer Ingelheim International GmbH, Edwards Lifesciences Corporation, Lilly, Janssen Pharmaceuticals, Inc, Merck & Co, Inc, Novo Nordisk A/S, NGM Biopharmaceuticals, ShouTi Inc, and VADovations, Inc (all paid to his institution); Dr Clark has received royalties or licenses from *Phenomix Sciences* and has patents planned, issued, or pending for intellectual property related to the Pheno-Diet: Individualized Lifestyle Intervention for Obesity Management Based on Obesity Phenotypes; Dr Madhavan has received a grant from Boston Scientific and consulting fees from Biotronik Inc (both paid to his institution); Dr Lopez-Jimenez has received consulting fees from K Health, Mediwhale Inc, and Wize-Care Technologies, has received honoria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from UpToDate, has received research grants from Select Research, the Dairy Management Incoporated and Novartis has patents planned, issued, or pending for multiple AI electrocardiography algorithm to detect low ejection fraction, has participated on the advisory boards for NewAmsterdam Pharma, anumana Inc, Ultrasite, Kento Health, and Novo Nordisk A/S. The other authors report no competing interests.

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Abbreviations and Acronyms: **AAA,** abdominal aortic aneurysm; **AF,** atrial fibrillation; **ASA,** acetylsalicylic acid; **ASCVD,** atherosclerotic cardiovascular disease; **BIA,** bioimpedance analysis; **BMI,** body mass index; **BP,** blood pressure; **CAC,** coronary artery calcium; **CAD,** coronary artery disease; **CKD,** chronic kidney disease; **CPAP,** continuous positive airway pressure; **CRF,** cardiorespiratory fitness; **CT,** computed tomography; **CTA,** CT angiography; **CVD,** cardiovascular disease; **DEXA,** dual-energy x-ray absorptiometry; **ECG,** electrocardiography; **FPG,** fasting plasma glucose; **GERD,** gastroesophageal reflux disease; **GFR,** glomerular filtration rate; **GLP-1RA,** glucagon-like peptide-1 receptor agonist; **HbA_{1c},** glycosylated hemoglobin; **HDL-C,** high-density lipoprotein cholesterol; **HF,** heart failure; **HFpEF,** HF with preserved ejection fraction; **HTN,** hypertension; **LDL-C,** low-density lipoprotein cholesterol; **MASLD,** metabolic dysfunction—associated steatotic liver disease; **MRI,** magnetic resonance imaging; **NSAID,** nonsteroidal anti-inflammatory drug; **NT-proBNP,** N-terminal pro-B-type natriuretic peptide; **ORG,** obesity-related glomerulopathy; **OSA,** obstructive sleep apnea; **PAP,** positive airway pressure; **SGLT2i,** sodium-glucose transport protein 2 inhibitor; **T2DM,** type 2 diabetes mellitus; **T_4,** thyroxine; **TSH,** serum thyrotropin; **WC,** waist circumference; **WHR,** waist-to-hip ratio

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