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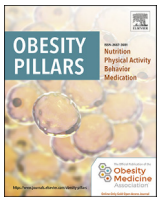

Review

Obesity, diabetes mellitus, and cardiometabolic risk: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2023

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ABSTRACT

Background: This Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) is intended to provide clinicians an overview of type 2 diabetes mellitus (T2DM), an obesity-related cardiometabolic risk factor.
Methods: The scientific support for this CPS is based upon published citations and clinical perspectives of OMA authors.
Results: Topics include T2DM and obesity as cardiometabolic risk factors, definitions of obesity and adiposopathy, and mechanisms for how obesity causes insulin resistance and beta cell dysfunction. Adipose tissue is an active immune and endocrine organ, whose adiposopathic obesity-mediated dysfunction contributes to metabolic abnormalities often encountered in clinical practice, including hyperglycemia (e.g., pre-diabetes mellitus and T2DM). The determination as to whether adiposopathy ultimately leads to clinical metabolic disease depends on crosstalk interactions and biometabolic responses of non-adipose tissue organs such as liver, muscle, pancreas, kidney, and brain.
Conclusions: This review is intended to assist clinicians in the care of patients with the disease of obesity and T2DM. This CPS provides a simplified overview of how obesity may cause insulin resistance, pre-diabetes, and T2DM. It also provides an algorithmic approach towards treatment of a patient with obesity and T2DM, with "treat obesity first" as a priority. Finally, treatment of obesity and T2DM might best focus upon therapies that not only improve the weight of patients, but also improve the health outcomes of patients (e.g., cardiovascular disease and cancer).

1. Introduction

Beginning in 2013, the Obesity Medicine Association (OMA) created and maintained an online Adult "Obesity Algorithm" (i.e., educational slides and eBook) that underwent yearly updates by OMA authors and was reviewed and approved annually by the OMA Board of Trustees [1]. This was followed by a similar Pediatric "Obesity Algorithm" with updates that occurred approximately every two years by OMA authors. The current OMA CPS regarding obesity and type 2 diabetes mellitus (T2DM) extensively expanded upon an initial draft derived from the 2021 OMA Adult Obesity Algorithm and is one of a series of OMA CPSs designed to assist clinicians in the care of their patients with the disease of obesity.

Fundamental to the understanding of obesity as a disease [2,3] is recognizing adipose tissue as more than an energy storage organ. Regarding energy storage, starvation of lean individuals may lead to death after about 60 days and a 35% weight loss. A patient with extreme obesity may survive prolonged fasting for as much as over one-year consuming acaloric fluids, vitamins and minerals, with a reduction in 60% body weight [4]. However, adipocytes and adipose tissue have vital functions well beyond energy storage alone. Disruption of healthy adipose tissue function leads to adverse health consequences such as hyperglycemia [5–9]. Positive caloric balance can lead to adipocyte hypertrophy, adipose tissue accumulation, and adipose tissue dysfunction (i.e., adiposopathy) – especially in the presence of limitations in unfettered adipocyte proliferation and differentiation of peripheral subcutanous adipose tissue. The adverse health consequences of adipose tissue immunopathies, endocrinopathies, and lipotoxicity contribute to the most common metabolic abnormalities encountered in clinical practice [2].

Among the adiposopathic consequences of obesity [2] are elevated

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Table 1
Ten takeaway messages regarding obesity and elevated blood glucose. [30] The adiposopathic consequences of obesity may promote hyperglycemia and the development of type 2 diabetes mellitus (T2DM). Higher doses of among the more effective anti-diabetes medications are undergoing cardiovascular disease (CVD) outcomes trials to determine potential CVD outcomes benefits when specifically used to treat obesity (i.e., highly effective anti-obesity medications [31]).

1.	The disease of obesity may have adiposopathic consequences that promote hyperglycemia [e.g., prediabetes and type 2 diabetes mellitus (T2DM)] [10].
2.	T2DM is a major risk factor for cardiovascular disease (CVD) [12,13].
3.	CVD (and cancer) are the most common causes of morbidity and mortality among patients with obesity and T2DM [11–14].
4.	Patients with obesity and T2DM should optimally undergo global CVD risk reduction (e.g., healthful nutrition and physical activity, weight reduction, smoking cessation, as well as optimal control of blood glucose, blood pressure, and blood lipids).
5.	Among patients with T2DM, administration of glucagon-like peptide-1 receptor agonists (GLP-1 RA), and/or sodium glucose transporter 2 (SGLT2) inhibitors may variably reduce body weight and reduce the risk for CVD events; administration of sulfonylureas and many insulins may increase body weight and may increase the risk for CVD events [16–19].
6.	Some GLP-1 RA are indicated to treat T2DM and reduce major adverse cardiovascular events (MACE) in patients with T2DM and established CVD (liraglutide, semaglutide, and dulaglutide). Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist and GLP-RA approved as an anti-diabetes medication [20]. Ongoing cardiovascular outcome studies are evaluating oral semaglutide in patients with T2DM (SOUL), semaglutide 2.4 mg SQ per week in patients with overweight or obesity (SELECT) [21], tirzepatide in patients with T2DM (SURPASS-CVOT), and tirzepatide in patients with obesity (SURMOUNT-MMO) [20].
7.	GLP-1 RA generally reduce body weight and improve other CVD risk factors [15,16] via mechanisms both dependent and independent of weight reduction [22], and represent a foundational mechanism integral to existing anti-obesity and anti-diabetes medications, as well as anti-obesity medications in development [20].
8.	In patients with T2DM, several SGLT2 inhibitors are indicated as anti-diabetes agents that may reduce major adverse CVD events, reduce heart failure, reduce cardiovascular death, reduce heart failure hospitalization, reduce renal disease progression, and in some cases, reduce overall mortality [23,24]; SGLT2 inhibitors may also modestly reduce body weight and blood pressure [16,25,26].
9.	Metformin may modestly reduce body weight in patients with diabetes mellitus [27], and may [28] or may not [29] decrease CVD among patients with diabetes mellitus [16].
10.	Several anti-diabetes medications are indicated to reduce CVD events. Some agents at higher doses that are specifically used as anti-obesity medications do not (yet) have CVD outcome data to support improved CVD risk reduction [16,20].

blood glucose, that clinically manifest as prediabetes and T2DM [10]. T2DM is a major risk factor for cardiovascular disease (CVD); CVD (and cancer) are the most common cause of morbidity and mortality among patients with obesity and T2DM [11–14]. Among patients with T2DM [90% with overweight/pre-obesity or obesity (https://www.cdc.gov/diabetes/data/statistics-report/risks-complications.html)], some anti-diabetes medications may reduce blood glucose, produce clinically meaningful body weight reduction, and reduce the risk of CVD [15,16]. Table 1 identifies ten takeaway messages regarding obesity and elevated blood glucose.

2. Overview of pathophysiology

According to the Obesity Medicine Association:

"Obesity is defined as a chronic, progressive, relapsing, and treatable multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences" [2].

Regarding adipose tissue dysfunction, adiposopathy can be defined as:

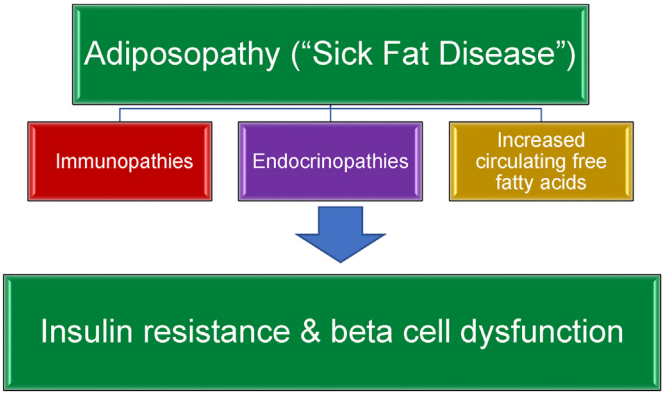

Fig. 1. How does obesity (adiposopathy) contribute to type 2 diabetes mellitus? In addition to biomechanical abnormalities leading to "fat mass disease" [2] obesity may cause adiposopathy, or "sick fat disease [34]." Adipose tissue immunopathies, endocrinopathies, and increased circulating free fatty acids may lead to insulin resistance and beta cell dysfunction [5–8,32,33]. The degree by which the adiposopathic consequences of obesity promotes hyperglycemia depends on the crosstalk, interactions, and biometabolic responses of other body organs such as liver, muscle, pancreas, kidney and brain.

"Adiposopathy is defined as pathogenic adipose tissue anatomic/functional derangements, promoted by positive caloric balance in genetically and environmentally susceptible individuals, that result in adverse endocrine and immune responses that directly and/or indirectly contribute to metabolic diseases (e.g., T2DM, hypertension, dyslipidemia, cardiovascular disease, and cancer)" [2].

Adiposopathy, also called "sick fat disease," can lead to immunopathies, endocrinopathies, and increased circulating free fatty acids, which in turn, may lead to insulin resistance and beta cell dysfunction [5–8,32,33]. A critical question for any clinician who manages patients with obesity and T2DM is: "How does obesity cause diabetes?" Figs. 1–3 provide an overview of how the adiposopathic consequences of obesity contributes to insulin resistance, pre-diabetes, and T2DM.

2.1. Definitions

2.1.1. Adipokines

Adipokines (i.e., adipocytokines) are cytokines produced by adipose tissue (i.e., secreted by adipocytes and adipose tissue stromal macrophages) involved in signaling relevant to energy balance, metabolic processes, and inflammation. Analogous to hepatokines from liver, myokines from muscle, and osteokines from bone, adipose tissue produces adipokines, such as leptin, adiponectin, tumor necrosis factor, visfatin, resistin, aprosin, and omentin, which affect glucose metabolism (See Figs. 2 and 3).

2.1.2. Adiponectin (previously "adipose most abundant gene transcript-1" or apM-1)

Adiponectin is the most abundant peptide primarily secreted by adipocytes. Adiponectin is anti-inflammatory. Among adiponectin's functions include improved insulin sensitivity, increased fatty acid oxidation, decreased fatty acid synthesis, decreased hepatic and muscle fat, reduced hepatic glucose production (i.e., decreased gluconeogenesis), increased muscle glucose uptake, and preservation of pancreatic β cell function (e.g., antiapoptotic properties), all leading to reduced development of diabetes mellitus and/or improved glucose levels. Low adiponectin concentrations are associated with diabetes, central obesity, insulin resistance and metabolic syndrome [57] (See Fig. 3).

2.1.3. C-Jun NH(2)-terminal kinase (JNK) pathway

Mitochondrial dysfunction (e.g., via adiposopathic tumor necrosis

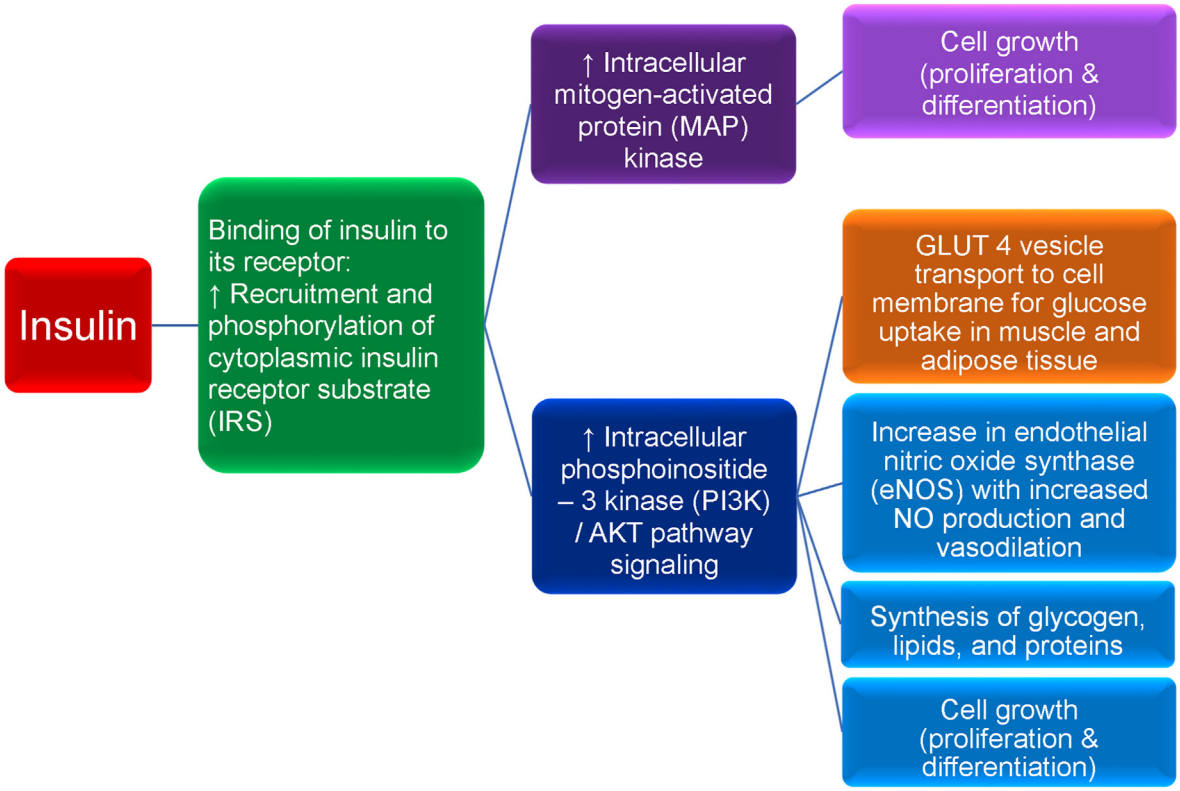

Fig. 2. Insulin and insulin receptor functions. Diminished insulin activity can be due to an absolute or relative decrease in circulating insulin and/or impaired insulin signaling via reduced number of insulin receptors and/or impaired post-receptor insulin signaling [22,28]. Normoglycemia can be maintained in the early stages of insulin resistance by increased basal insulin (i.e., hyperinsulinemia), as often occurs in patients with obesity. However, over time, insulin secretion may no longer be sufficient to overcome insulin resistance, resulting in hyperglycemia. Obesity and the hyperglycemia of type 2 diabetes mellitus (T2DM) may result in a relative decrease in pancreatic insulin secretion, potentially due to elevations in leptin levels [35] as well as due to apoptosis with decreased pancreatic beta cell mass [4] as the result of: (a) beta cell exhaustion/overload [36], (b) glucolipotoxicity [4,37], (c) increase in pro-inflammatory factors, and (d) decrease in anti-inflammatory factors (e.g., adiponectin) [38]. Insulin is a peptide hormone released by pancreatic beta cells in response to a rise in blood glucose (e.g., postprandial response to carbohydrate ingestion). Fructose, some amino acids and fatty acids can also augment insulin release [39]. Insulin binds to the extracellular alpha subunit portion of the transmembrane insulin cellular receptor of body tissues (e.g., liver, muscle, fat, brain). This activates a phosphorylation cascade involving transmembrane insulin receptor beta subunits that process tyrosine kinase activity, auto-phosphorylating insulin receptor tyrosines, and promoting the phosphorylation and activation of cytoplasmic insulin receptor substrate (IRS). Activated IRS stimulates intracellular mitogen-activated protein (MAP) kinase, which in turn, promotes cell growth (e.g., proliferation and differentiation of tissues such as skeletal muscle cells [40] and fat cells [41]). While insulin mainly functions as a physiologic mitogenic facilitator, hyperinsulinemia may predispose to unregulated mitogenesis and cancer [42–44] Insulin-mediated phosphorylation of IRS also facilitates the phosphoinositide 3-kinase (PI3K)/AKT pathway (i.e., AKT is also known as protein kinase B) which is responsible for most of insulin's metabolic effects – such as the transport of glucose vesicle transporters (GLUT 4) to outer cellular membranes resulting in glucose uptake from the circulation into body tissues – thus lowering blood glucose. Insulin-dependent GLUT 4 is found in skeletal muscle and adipose tissue; insulin-independent GLUT 2 is found in liver. Increased PI3K/AKT signaling also promotes (a) increase in endothelial nitric oxide synthase (eNOS) that facilitates increased nitric oxide production, increased vasodilation, and increased adipose tissue perfusion allowing for enhanced glucose and free fatty acids uptake in adipocytes for storage, (b) synthesis of glycogen, lipids, and proteins and (c) cell growth (i.e., proliferation & differentiation). Dysregulation of the PI3K-AKT pathway for cell proliferation/differentiation is the most common activated pathway in human cancer [44,45]. Among patients with obesity and T2DM, in addition to reduced number of insulin receptors potentially as the result of impaired insulin receptor delivery to the cell surface due to endoplasmic reticulum stress, severe insulin resistance is mainly described as a post insulin receptor signaling defect, via disruption of the IR/IRS cascade. Specifically, obesity may result in adiposopathic increases in inflammatory factors (e.g., cytokines such as tumor necrosis factor and interleukins) and free fatty acids that may impair PI3K/AKT signaling, potentially contributing to post-receptor insulin resistance, prediabetes, and/or T2DM [46].

factor and "toxic" intracellular fatty acids) increases intraorganelle stress, increases reactive oxygen species, and increases intracellular JNK, which promotes serine phosphorylation of the insulin receptor substrate (IRS). Serine phosphorylation of IRS impairs tyrosine kinase phosphorylation of IRS and diminishes insulin signaling via the phosphoinositide 3-kinase /protein kinase B (PI3K/AKT) pathway, leading to post-receptor insulin resistance (See Fig. 2).

2.1.4. Cytokines

Cytokines are small proteins made by immune cells (e.g., T helper cells and macrophages) and other tissues (e.g., adipocytes) that facilitate cell signaling relevant to cell/tissue growth, migration, differentiation, and inflammation. General examples of body cytokines include tumor necrosis factor (i.e., regulates cellular immune and metabolic response), chemokines (i.e., chemoattractants that direct cell migration, adhesion, and activation), interferons (i.e., antiviral proteins), interleukins (i.e., regulate pro- and anti-inflammatory responses), growth factors (i.e., promote cell division and differentiation), and colony stimulating factors (i.e., bind to hemopoietic stem cells and direct intracellular signaling pathways leading to cellular proliferation and differentiation into a specific kind of blood cell) (See Figs. 2 and 3).

2.1.5. Extracellular vesicles (e.g., exosomes, microvesicles, and apoptotic bodies)

Small adipocyte membrane vesicular structures are sometimes released that serve as mediators for long-distance cell-to-cell communications. Release of extracellular vesicles may occur during adipocyte senescence (e.g., aging of adipocytes), or as a consequence of

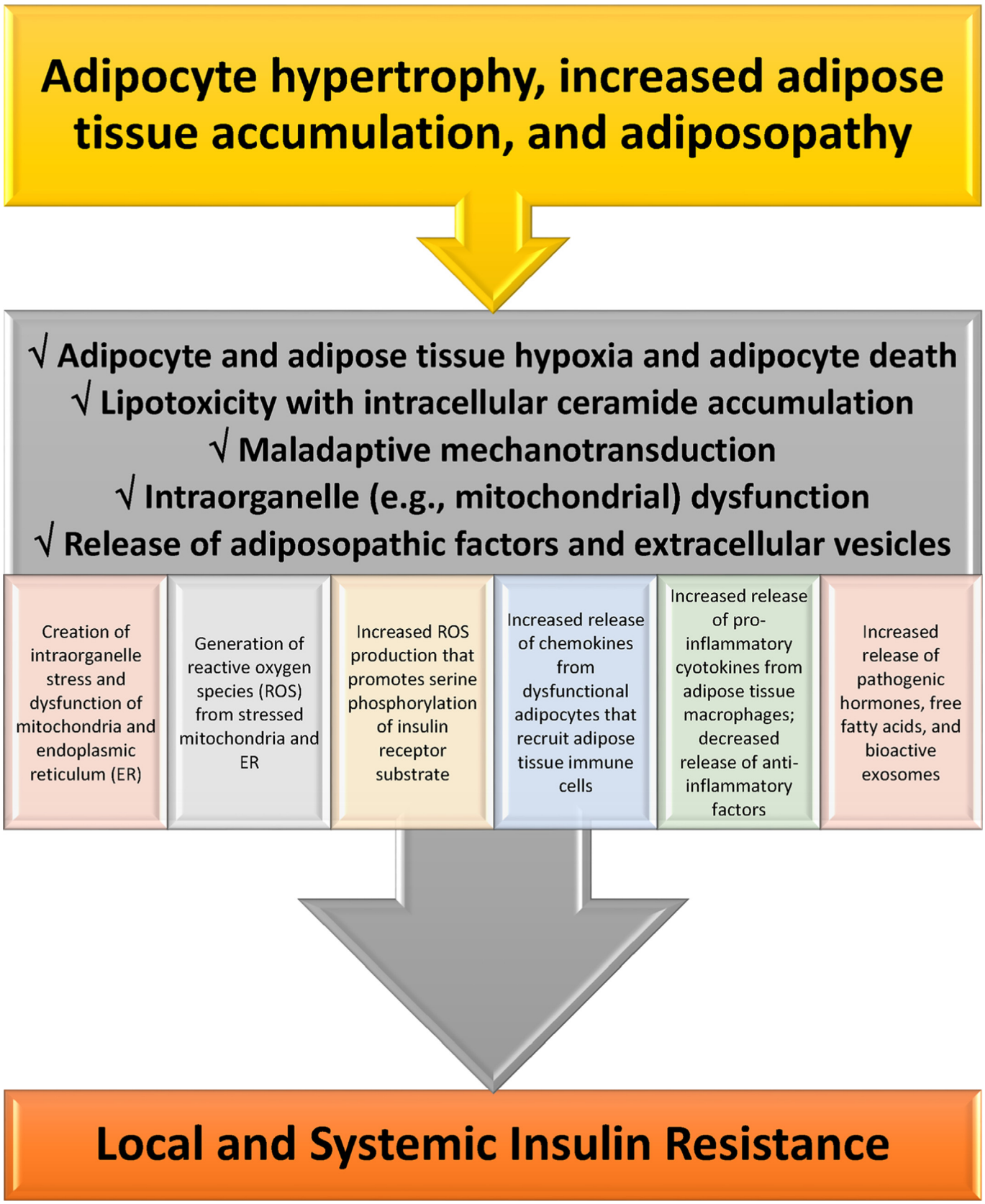

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Fig. 3. Mechanisms how adiposopathic processes lead to insulin resistance. If obesity-mediated adipocyte hypertrophy and adipose tissue accumulation outgrows vascular supply, then the insufficient delivery of oxygen may contribute to adipocyte and adipose tissue hypoxia and increased adipocyte death. Adipocyte and adipose tissue hypoxia may adversely affect multiple metabolic processes regarding angiogenesis, adipocyte proliferation, adipocyte differentiation, reactive oxygen species generation, inflammation, and fibrosis. Beyond adipocyte and adipose tissue hypoxia, excessive intracellular lipids in the form of fatty acids may lead to ceramide (i.e., a unit of sphingolipids) and diacylglycerol (DAG) formation in adipocytes, where similar to adverse effect of increased fatty acid influx and ceramide and DAG accumulation in liver and muscle, may cause lipotoxicity leading to adipocyte dysfunction [47], such as: (a) inhibiting AKT Protein Kinase B and thus decreasing glucose uptake via GLUT 4, (b) inhibiting hormone sensitive lipase and thus decreasing adrenergic-mediated lipolysis, and (c) impairing mitochondrial function [47], all contributing to insulin resistance. Mechanotransduction occurs when cells sense, integrate, and respond to mechanical stimuli via biologic signaling and adaptations. During healthful expansion, adipose tissue responds by adapting to its microenvironment (e.g., formation, dissolution, and reformation of extracellular matrix) via continuous remodeling to maintain its structural and functional integrity. During positive caloric balance, especially if proliferation is impaired, adipose tissue expansion is often accompanied by hypertrophy of existing adipocytes. Adipocyte hypertrophy, immune cells infiltration, fibrosis and changes in vascular architecture may generate mechanical stress on adipose cells, alter healthful adaptive mechanotransduction, and disrupt healthful adipose cell expansion physiology. Maladaptive mechanotransduction may promote obesity-associated dysfunction in adipose tissue (i.e., adiposopathy) [48]. Overall, contributors to mitochondrial dysfunction include adipocyte and adipose tissue hypoxia, lipotoxicity [47,49], maladaptive mechanotransduction, hyperglycemia [50], and high fat dietary intake [51]. Adipocyte mitochondrial dysfunction is a potential primary cause of adipose tissue inflammation [52]. Among the adverse consequences of adiposopathic mitochondrial (and endoplasmic reticulum) dysfunction is the generation of reactive oxygen species (ROS). ROS are unstable molecules containing oxygen that easily react with other cellular molecules, contributing to deoxynucleic acid damage, cancer, fibrosis, and aging [44]. Other contributors to increased ROS production are hyperglycemia [53] and adiposopathic increases in cytokines such as tumor necrosis factor. Increased tumor necrosis factor-mediated mitochondrial ROS production may facilitate JNK activation, increase serine phosphorylation of insulin receptor substrate-1 (IRS-1), decrease insulin-stimulated tyrosine phosphorylation of IRS-1, and thus contribute to obesity-mediated insulin resistance [54,55]. In summary, adipocyte hypertrophy leading to initial adipocyte dysfunction results in local proinflammatory effects that, in turn, further worsen adipocyte function, resulting in worsening adiposopathy and adipocyte insulin resistance. Systemically, adiposopathic proinflammatory factors, pathogenic hormones, and free fatty acids may be released into the circulation either directly from adipose tissue, or via adipocyte extracellular vesicles (e.g., bioactive molecules such as lipids, proteins, and nucleic acids that are packaged and transferred from adipocytes to other body tissues via exosomes, microvesicles, and apoptotic bodies formed as the result of adipocyte necroptosis or pyroptosis). The increase in pro-inflammatory factors (e.g., tumor necrosis factor and interleukins 1 beta and 6) [56] and decrease secretion of anti-inflammatory factors (e.g., adiponectin) [57] may promote insulin resistance (i.e., reduced cellular surface insulin receptors and post-insulin receptor defects) in susceptible non-adipose tissue peripheral organs, such as skeletal muscle and liver, contributing to "inflexibility" in managing, responding or adapting to changes in metabolic substrates.

programmed cell death such as: (a) apoptosis (i.e., programmed cell death without inflammatory response), (b) necroptosis (i.e., programmed cell death with inflammatory response), and (c) pyroptosis (i.e., cell death due to inflammation). Once released, these extracellular vesicles can transfer various bioactive molecules (e.g., lipids and proteins), such as encapsulated cytokines and genetic information (e.g., micro ribonucleic and deoxyribonucleic acids) from their parental cells (i.e., adipocytes) to distant target cells [29]. In patients with obesity, adipocyte-derived exosomes promote pro-inflammatory polarization of M1 and M2 macrophages and may also affect non-adipose tissue organs (e.g., muscle and liver) [30] (See Fig. 3).

2.1.6. *Free fatty acids*

Biologically relevant lipids include triglycerides (e.g., saturated, monounsaturated, and polyunsaturated), phospholipids (e.g., glycerophospholipids and sphingolipids), and sterols (e.g., cholesterol in animals and phytosterols in plants). Triglycerides are fat esters with three individual fatty acids attached to each of the 3 carbons of one molecule of glycerol. Free fatty acids are formed when triglycerides, such as those stored in adipocytes, undergo lipolysis (i.e., triacylglycerol hydrolysis), with the release of "free" fatty acids into the circulation that are subsequently bound to albumin. While adipocyte uptake of free fatty acids can occur directly from the circulation [58], adipocyte uptake of fatty acids for triglyceride formation and storage is mostly described via interactions with circulatory triglyceride rich lipoproteins (e.g., chylomicrons from the intestine and very low density lipoproteins from the liver). After meals, while in the nutrient absorptive state, insulin secreted by the pancreas: (a) increases lipoprotein lipase activity which promotes lipolysis of very low-density lipoproteins and chylomicrons and promotes free fatty acid uptake by adipocytes [59], and (b) increases diacylglycerol acyltransferase activity, which catalyzes fatty acid esterification to glycerol (forming triacylglycerol or triglycerides), which is derived from insulin-mediated glucose uptake [60]. The post-meal, insulin mediated increased uptake of fatty acids, coupled with insulin's antilipolytic effects (e.g., decreased adipocyte hormone sensitive lipase activity) accounts for decreased fatty acid blood levels after meals (compared to increased free fatty acids in the postabsorptive state), which is an effect that may be blunted in patients with insulin resistance and type 2 diabetes mellitus and inadequate suppression of post-meal free fatty acid levels [61].

In the postabsorptive fasting state (during times of lower insulin levels), cortisol, catecholamines, and growth hormone promote adipose tissue lipolysis by stimulating adipose triglyceride lipase and hormone sensitive lipase activity [59], and thus increasing circulatory free fatty acid levels. Lipotoxicity occurs when chronically elevated circulating fatty acids accumulate in non-adipose tissues (e.g., liver and muscle), and adversely affect body tissue function (See Fig. 3). Regarding origin of intra-organ lipids, in patients with obesity and nonalcoholic fatty liver disease, at least one study suggests that the origin of hepatic triglycerides were approximately 60% from circulating non-esterified free fatty acids, 25% from de novo lipogenesis, and 15% from the diet [62]. The clinical relevance is that obesity-mediated fatty liver is an important cause of insulin resistance, with most patients with obesity having nonalcoholic fatty liver disease (50–90%) [63]and the prevalence of non-alcoholic fatty liver disease among patients with type 2 diabetes mellitus being approximately 60% [64]. Conversely, the prevalence of obesity in patients with nonalcoholic fatty liver disease is about 50% [65,66] and the prevalence of diabetes mellitus among those with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis being approximately 22 and 44% respectively [67]. Thus, the majority of patients with obesity and diabetes have fatty liver, while 50% or less of patients with fatty liver have obesity or diabetes mellitus – owing to the many different cause of fatty liver [65]. In short, free fatty acids delivered to the liver can be stored as non-toxic esterified triglycerides, broken down via betaoxidation to produce energy, packaged in very low density lipoproteins and released into the circulation, or accumulate to form toxic ceramides and diacylglycerols.

2.1.7. *Hormone sensitive lipase (HSL)*

Adipose triacylglycerol lipase (ATGL) and HSL account for over 95% of lipolytic triglyceride hydrolase activity in white adipose tissue. Lipolysis via HSL (located in adipocytes) is stimulated by catecholamines and inhibited by insulin (See Fig. 3).

2.1.8. *Insulin receptor (IR)*

The insulin receptor is a transmembrane protein that binds to insulin and insulin-like growth factors and facilitates cellular signaling largely through tyrosine kinase activation. Insulin is an anabolic peptide hormone secreted into the circulation by pancreatic beta cells. Insulin-like

Fig. 4. Illustrative adipose tissue functions potentially altered by obesity-mediated immunopathies. Adipose tissue is an active immune (and endocrine organ) that regulates multiple body processes critical to body homeostasis and body health. Disruption of adipose immune functions (i.e., adiposopathy) contributes to metabolic diseases and adverse cardiac and cancer outcomes. Many of the cytokines released with obesity may act locally. Systemic cytokine effects depend upon individual responses of non-adipose tissue organs [4].

growth factors (IGF) are secreted by tissues such as liver and pituitary. IR's are found in virtually all body tissues, including adipocytes, liver cells, muscle cells, pancreatic beta cells, kidney cells, and brain cells. Upon extracellular insulin binding to the two IR alpha subunits, the two IR transmembrane beta units auto-phosphorylate, and activate tyrosine kinase, which recruits and phosphorylates intracellular insulin receptor substrates (IRS) for transmission of intracellular metabolic signals (e.g., synthesis of glycogen, lipids, and proteins, promotion of cell proliferation/differentiation, and production of endothelial nitric oxide synthesis with vasodilation).

In the muscle, heart, and adipose tissue, insulin-mediated signaling from activated insulin receptors: (a) promotes intracellular recruitment of insulin dependent glucose 4 transporters (GLUT-4) derived from intracellular vesicles, (b) facilitates the translocation of intracellular GLUT-4 transporters to the plasma membrane via targeted exocytosis, (c) increases glucose cellular uptake, and (d) thus decreases circulating glucose levels. Regarding adipose tissue, insulin increases glucose uptake in adipocytes, with increased lipogenesis (i.e., cytoplasmic glycolysis leading to acetyl-CoA formation with subsequent fatty acid and triglyceride synthesis), decreased lipolysis (i.e., decreased adipocyte hormone sensitive lipase activity with decreased triglyceride hydrolysis), and increased fat mass. In muscle, insulin increases glucose uptake (i.e., skeletal muscle is the principal tissue responsible for insulin-stimulated glucose disposal), increases glycogen synthesis, decreases glucose release, and increases lipogenesis.

In the liver, pancreatic beta cells, kidney and brain, glucose transport is not directly dependent on insulin. Instead, glucose transport in the liver, pancreatic beta cells, and kidney occurs via insulin independent GLUT2, while in the brain, glucose transport occurs via insulin independent GLUT 1 & GLUT 3. However, insulin maintains its other functions in these tissues by activation of insulin receptors, promoting glycogen synthesis in the liver (as also occurs in muscle), and decreasing gluconeogenesis in liver (i.e., little gluconeogenesis occurs in muscle and brain). While muscle stores the greatest amount of body glycogen [68], during basal conditions, it is the liver that is the main organ for glucose regulation via endogenous glucose production by glycogenolysis and gluconeogenesis [69]. About 80% of glucose production is derived from gluconeogenesis and glycogenolysis by the liver, and about 20% is

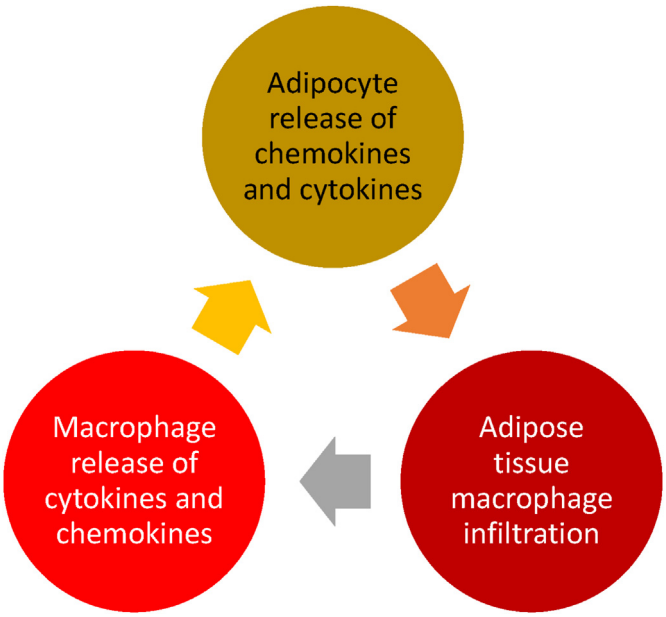

Fig. 5. Obesity and the adiposopathic inflammatory cycle. Adipocyte hypertrophy and adipose tissue accumulation may lead to relative or absolute hypoxia, lipotoxicity, altered mechanotransduction, and intraorganellar dysfunction prompting release of cytokines (e.g., tumor necrosis factor) and chemokines [e.g., monocyte chemoattractant protein-1 (MCP-1)]. Adipocyte secreted MCP-1 attracts monocytes to adipose tissue that differentiate into macrophages. Adipose tissue macrophages produce additional MCP-1, that recruits more inflammatory cells to adipose tissue. Adipose tissue macrophages also produce proinflammatory cytokines such as tumor necrosis factor, that among pathogenic effects, includes the promotion of MCP-1 production from adipocytes, recruiting yet more immune cells to adipose tissue.

derived from gluconeogenesis by the kidneys [4,70] In lean individuals, both glycogenolysis and gluconeogenesis contribute equally to total endogenous glucose production, with the contribution of gluconeogenesis being higher in individuals with obesity or type 2 diabetes [4]. Thus, in patients with obesity and T2DM, ***fasting*** hyperglycemia is largely due to an increase in hepatic gluconeogenesis. Conversely, in patients with prediabetes and T2DM, ***postprandial*** hyperglycemia is due to decreased glucose disposal in insulin resistant peripheral tissues (i.e., muscle) and decreased suppression of gluconeogenesis after meal ingestion (i.e., liver) [4,71]. Regarding the brain, insulin decreases hunger and plays a role in development, neuroprotection, metabolism, and plasticity [72].

2.1.9. Insulin receptor substrates (IRS)

IRS are intracellular/cytoplasmic adapter proteins. Upon extracellular binding of insulin to the insulin receptor, insulin receptors are activated by phosphorylation, causing IRS to also undergo phosphorylation. IRS transmit signals via intracellular pathways applicable to glucose uptake and cell growth [e.g., mitogen-activated protein (MAP) kinase and enzymes related to the phosphoinositide–3 kinase (PI3K) /AKT pathway]. Phosphorylation of the tyrosine residue of insulin receptor substrate (IRS) activates IRS and facilitates intracellular insulin signaling. Phosphorylation of the serine residue of IRS impairs IRS activity and diminishes intracellular insulin signaling. Factors that may increase the serine phosphorylation of IRS (and thus contribute to post-receptor insulin resistance) include activation of JNK by free fatty acids, inflammation (i.e., tumor necrosis factor), and cellular stress (See Figs. 2 and 3).

2.1.10. Insulin resistance

Beyond a decrease in the number of insulin receptors, diminished insulin effect on body tissues in patients with obesity and T2DM is mostly due to adiposopathic abnormalities in post-receptor insulin signaling, as might occur via inflammation, lipotoxicity, and pathogenic effects of alterations in mechanotransduction. Direct measures of insulin resistance include insulin suppression test/insulin/glucose clamp techniques. Euglycemic-hyperinsulinemic clamp studies support obesity as negatively associated with rates of glucose uptake in skeletal muscle, adipose tissue, and liver. The rates of glucose uptake in skeletal muscle and adipose tissue are strongly correlated, as is the rate of whole-body glucose uptake [31]. Beyond definitive insulin clamp techniques, inferential, indirect, and less precise measures of insulin resistance include fasting glucose and hemoglobin A1c, as well as oral glucose tolerance testing, fasting insulin levels, and homeostatic model assessment for insulin resistance (HOMA-IR) or quantitative insulin-sensitivity check index (QUICKI). HOMA-IR and QUICKI are calculations involving fasting glucose and fasting insulin levels.

2.1.11. Interleukins

Interleukins (IL) are glycoprotein cytokines produced by leukocytes for regulating immune responses that can be pro-inflammatory (e.g., IL 1) or anti-inflammatory (e.g., IL 10). Interleukin 6 can be either pro-inflammatory or anti-inflammatory (See Fig. 3).

2.1.12. Leptin

Leptin is a peptide hormone adipocytokine predominantly made by adipocytes (and enterocytes) that regulates food intake, body mass, and reproductive function and plays a role in fetal growth, proinflammatory immune responses, angiogenesis, and lipolysis (See Fig. 2).

2.1.13. Lipotoxicity

Excessive intracellular lipid influx of circulating free fatty acids may lead to ceramide (i.e., a unit of sphingolipids) and diacylglycerol formation in body tissues such as adipocytes, muscle, and liver. Ceramides are a heterogeneous group of bioactive membrane sphingolipids that with obesity, depending on characteristic fatty acyl chain lengths and subcellular distribution, may accumulate and cause cell-type-specific lipotoxic reactions that disrupt metabolic homeostasis and lead to the development of cardiometabolic diseases [32]. Beyond adipocyte and adipose tissue hypoxia and maladaptive mechanotransduction, intraorganelle (e.g., mitochondria) and cellular dysfunction may occur due to the detrimental effect of intracellular lipids – termed "lipotoxicity" [33] (See Fig. 3). During positive caloric balance, the adverse consequences of adiposopathy include unhealthy adipose tissue expansion (e.g., relative impairment of adipocyte proliferation, increased adipocyte hypertrophy, and inflammation contributing to decreased insulin sensitivity [34]). Both limitations in the ability of adipocytes to adequately store excess energy in lipid droplets and onset of insulin resistance may result in "energy overflow" in the form of increased circulating fatty acids. As with adipocytes, increased free fatty acid influx to non-adipose body tissues such as muscle and liver result in the increased storage of long-chain non-esterified fatty acids and formation of "toxic" products such as ceramides, diacylglycerols (DAGs), and saturated fatty acids, which can induce chronic inflammation, mitochondrial dysfunction, and insulin resistance [35]. In fact, rather than the amount of free fatty acids delivered to body tissues, it is the intracellular metabolism of fatty acids specific to the individual, which may best correlate to the production of toxic products (e.g., reactive oxygen species, diacylglycerol, and ceramides) which result in adverse effects on biometabolic functions [30] (See Fig. 3).

2.1.14. Mechanotransduction

Mechanotransduction occurs when cells sense physical stimuli, and then respond with alterations/adaptations in biological outcomes, such as (mal)adaptations in adipocyte or adipose tissue growth due to adipocyte hypertrophy or increase in total fat mass. During positive caloric balance, adipocyte hypertrophy, and adipose tissue expansion, adipose tissue mechanosensing processes help guide structural remodeling, providing the scaffolding needed to support expanded adipocytes

Fig. 6. Illustrative adipose endocrine functions. Adipose tissue is an active endocrine (and immune) organ that regulates multiple body processes critical to body homeostasis and health. Adipocytes have cellular receptors for traditional hormones, nuclear receptors for other hormones, receptors for cytokines or adipokines, receptors for neuronal hormones, as well as receptors for adenosine, lipoproteins, neuropeptide Y1 and Y5, prostaglandins, vascular endothelial growth factor and endocannabinoids. Dysfunction of adipose tissue (adiposopathy) may lead to adverse endocrinopathies and immunopathies leading to adverse clinical outcomes (e.g., diabetes mellitus, hypertension, dyslipidemia, alterations in reproductive hormones, cardiovascular disease, and cancer).

and adipose tissue [4]. This results in mechano-regulation processes that include the deposition, rearrangement, removal and reformation of matrices to maintain overall form and function [36]. During positive caloric balance, impaired adipogenesis [37] along with impaired adipose tissue matrix adaptation may limit adipose tissue expandability (i.e., impairing adipose tissue energy storage and function), and thus contributing to metabolic diseases such as T2DM [38] (See Fig. 3).

2.1.15. Metabolic inflexibility

Metabolic flexibility is the ability of the organ to respond or adapt to changes in metabolic substrates, as routinely occurs during cycles of eating and fasting. Just as adipokines affect metabolic flexibility in adipocytes, myokines and hepatokines act on metabolism through paracrine and endocrine signaling in the muscle and liver. An inability to adequately metabolize the adiposopathic increased circulatory free fatty acid influx may contribute to nonalcoholic fatty liver disease, resulting in lipotoxicity, mitochondrial dysfunction, and cellular stress which leads to liver inflammation, apoptosis and fibrogenesis. Similarly, adiposopathic-mediated systemic insulin resistance may cause skeletal muscle to be "inflexible" in its metabolism of glucose, with accompanying mitochondrial dysfunction and decreased mitochondrial oxidation of free fatty acid influx re-routing fatty acids towards ceramide synthesis in skeletal muscle (as also occurs in the liver), further worsening insulin signaling and contributing to worsening of insulin resistance and thus contributing to obesity-mediated prediabetes or T2DM (See Fig. 3).

2.1.16. Mitogen-activated protein (MAP) kinase

Mitogens are proteins that promote mitosis (cell division). MAP kinases are intracellular proteins that communicate receptor signals to the cell nucleus to help regulate cell proliferation, differentiation, and cellular death (See Fig. 2).

2.1.17. Phosphoinositide-3-kinase (PI3K) /AKT pathway

Phosphoinositide-3-kinase and AKT (protein kinase B) are intracellular signal enzymes involved in glucose homeostasis and cell growth. Postprandial increases in glucose levels (e.g., via intestinal absorption of

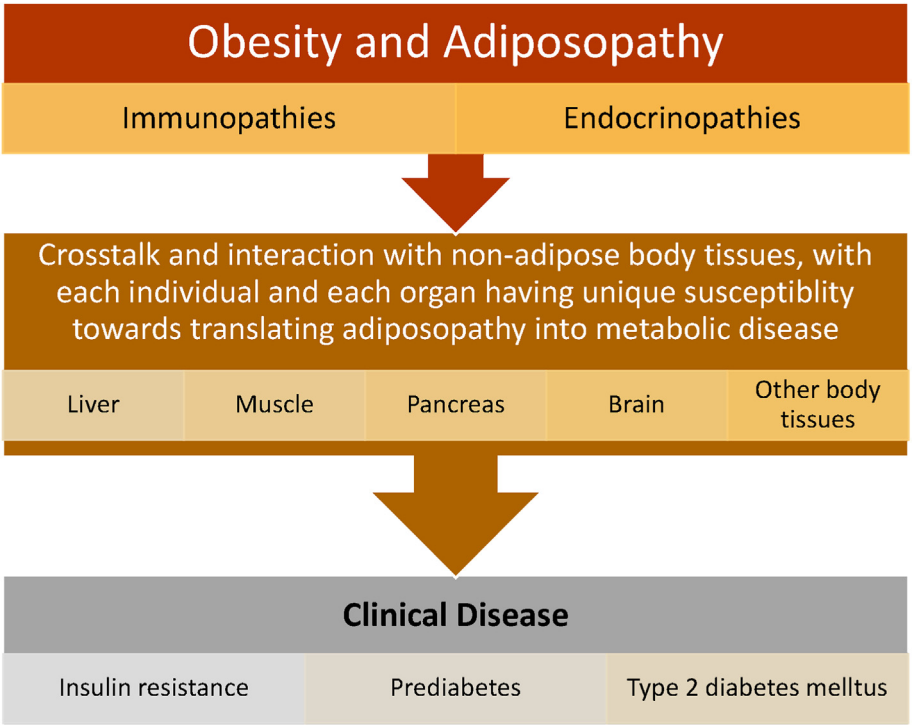

Fig. 7. Importance of non-adipose tissue in obesity-related glucose dysregulation (and other cardiometabolic diseases). The degree the immunopathies and endocrinopathies of adiposopathy result in adverse clinical consequences (e.g., abnormalities in glucose metabolism) largely depend on crosstalk, interactions, and biometabolic responses from non-adipose body tissues. Prediabetes and type 2 diabetes mellitus (T2DM) are mostly caused by multi-organ insulin resistance in conjunction with a decline in pancreatic beta cell insulin secretory function [4] The degree that weight reduction improves body organ function (e.g., adipose tissue, liver, muscle, pancreas, kidney, brain) varies among different individuals and among different organs within the individual. For example, insulin sensitivity in the liver (insulin-mediated suppression of glucose production) and adipose tissue (insulin-mediated suppression of lipolysis) may be maximally improved with 5%–8% weight reduction, while greater amounts of weight reduction may further improve skeletal muscle insulin sensitivity [4].

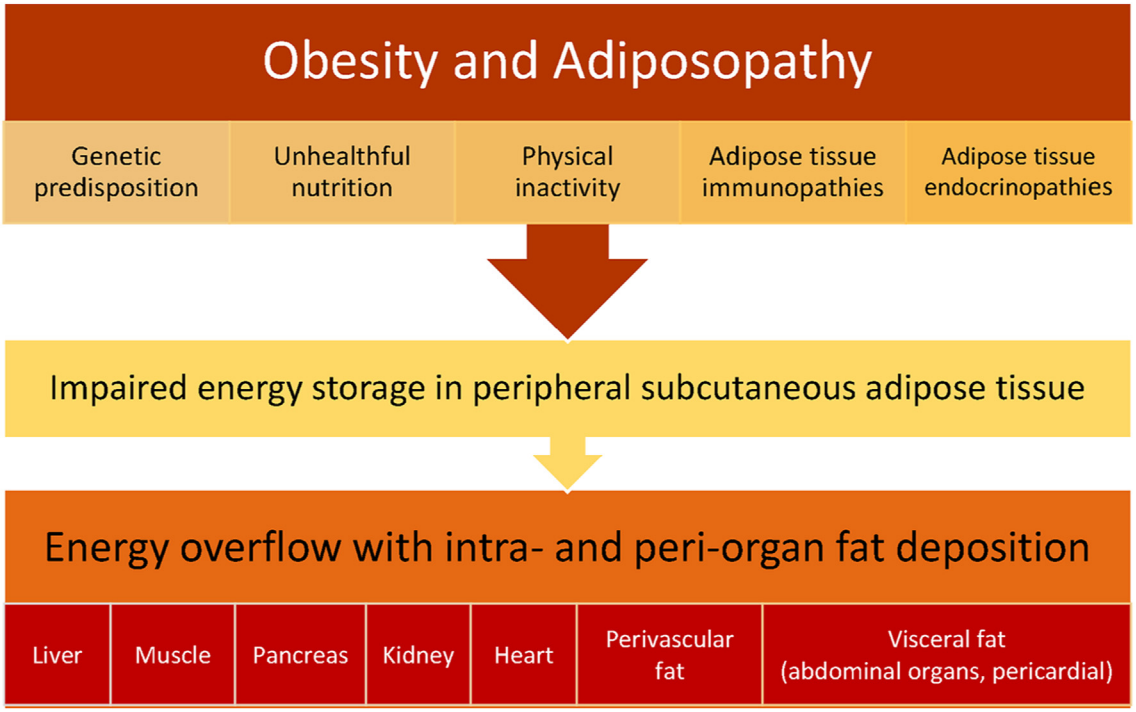

Fig. 8. Obesity, adiposopathy, energy overflow, and fat deposition within and around body organs. If during positive caloric balance, energy is stored in peripheral subcutaneous adipose tissue through unfettered adipocyte proliferation and differentiation, then while this may still result in biomechanical obesity complications described by "fat mass disease," this may mitigate the adiposopathic "sick fat disease" immunopathies and endocrinopathies. However, if during positive caloric balance, either adipocyte proliferation or differentiation is impaired, then this may cause adipose tissue dysfunction (See Fig. 3) and limit energy storage in adipose tissue. This may result in immunopathies (See Fig. 4), endocrinopathies (See Fig. 6), and energy overflow with fat that may be deposited within and around body organs (i.e., fatty liver, fatty muscle, fatty heart), potentially resulting in "lipotoxicity" (See Fig. 3), depending on the susceptibility of the non-adipose tissue organ (See Fig. 7). The determination of energy (i.e., fat) storage distribution during positive caloric balance within the individual is dependent upon such factors as age [14], sex [14], race [14], genetics, medications (e.g., hormones, thiazolidinediones [98]), and concurrent illnesses (e.g., lipodystrophy). In general, among patients with overweight/pre-obesity and/or obesity undergoing weight reduction interventions, subcutaneous adipose tissue undergoes the greatest absolute amount of fat mass reduction through healthful nutrition, routine physical activity, anti-obesity medications, and bariatric surgery, largely because subcutaneous adipose tissue usually makes up most body fat (i.e., 90% or more). That said, the reduction of visceral adipose tissue correlates with reduction of subcutaneous adipose tissue, and the proportion of visceral fat reduction is often greater than subcutaneous fat reduction [99], with the degree of percent visceral fat reduction influenced by the same beforementioned factors that originally contributed to visceral fat accumulation.

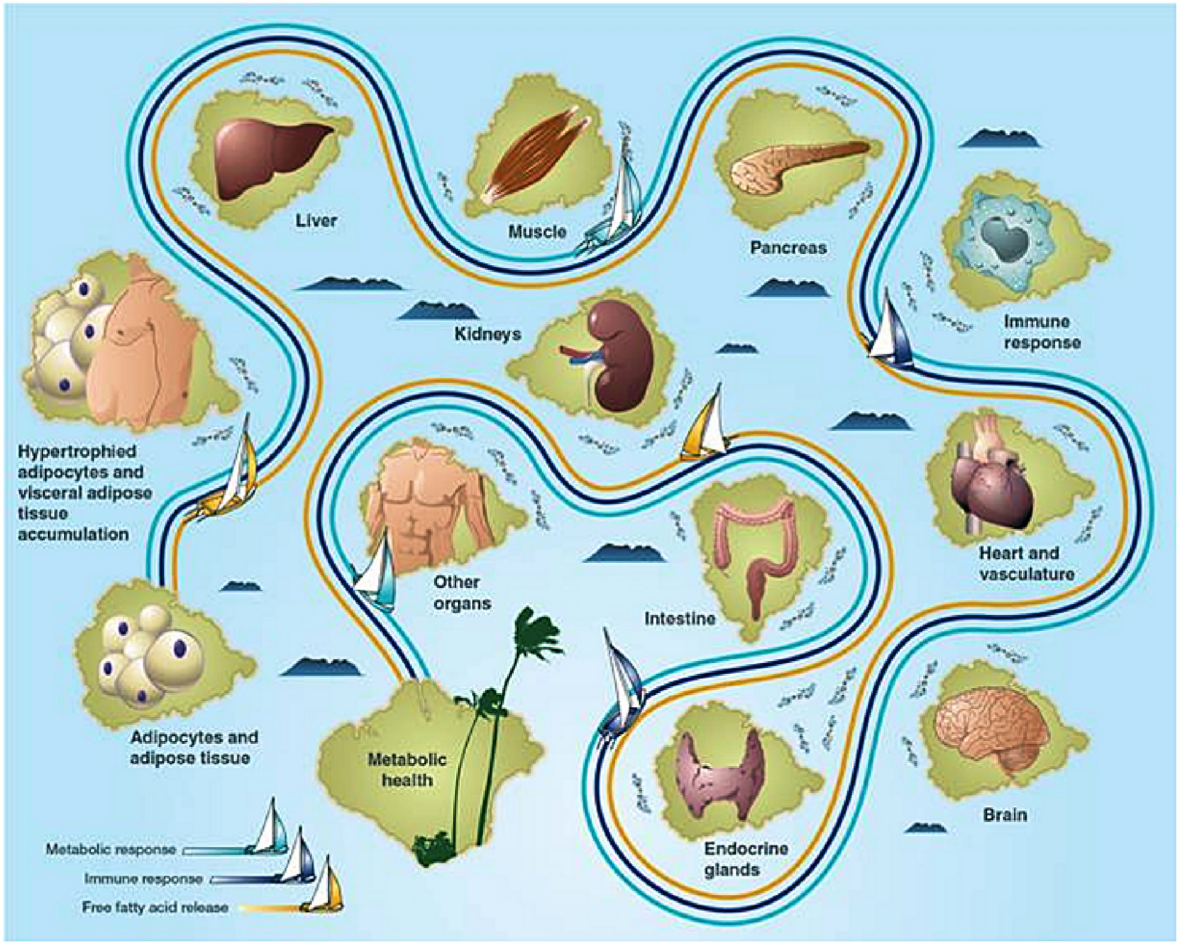

Fig. 9. Navigating potential adiposopathic health consequences of adipocyte hypertrophy and visceral adiposity. Obesity, adipocyte hypertrophy, and accumulation of adipose tissue in the visceral and android regions often reflects pathogenic adipose tissue immune and endocrine responses, as well as increased circulating free fatty acids, that may be lipotoxic to peripheral organs. The pathogenic potential of adipose tissue to cause clinical disease largely depends on crosstalk, interactions, and responses of multiple body tissues. The liver, muscle, and other body organs among unique individuals may elicit unique responses to physiological/pathophysiological interaction and crosstalk with their adipose tissue (e.g., the adiposopathic immune, endocrine, and fatty acid onslaught that often occurs with obesity). Body organ metabolic flexibility is the ability of the organ to respond or adapt to changes in metabolic substrates. Adipokines influence metabolic flexibility in adipocytes. Similarly, myokines and hepatokines act on metabolism in muscle and liver, respectively, through paracrine and endocrine signaling [100]. Thus, the predisposition towards developing nonalcoholic fatty liver disease, for example, might best be explained by a "multiple hit" model. Beyond the immunopathies, endocrinopathies, increased free fatty acids, and insulin resistance consequences of adiposopathy, contributors to nonalcoholic fatty liver disease also include qualitative nutritional factors, physical inactivity, gut microbiota, concomitant medications, and especially genetic and epigenetic factors [65,101] An inability to adequately metabolize adiposopathic free fatty acid overload (i.e., hepatic metabolic inflexibility) is key towards the development of nonalcoholic fatty liver disease, with lipotoxicity, mitochondrial dysfunction and cellular stress leading to inflammation, apoptosis and fibrogenesis [102].Similarly, insulin sensitivity in skeletal muscle differs, depending on genetic predisposition [103]. Skeletal muscle accounts for about 70% of insulin-mediate glucose disposal [104]. Potentially as the result of adiposopathic insulin resistance, not only might skeletal muscle be "inflexible" in its metabolism of glucose (thus contributing to hyperglycemia), but mitochondrial dysfunction and decreased mitochondrial oxidation of free fatty acid influx from adiposopathy may re-route fatty acids towards ceramide synthesis in skeletal muscle, further worsening insulin signaling and contributing to worsening of insulin resistance [105] and thus contributing to obesity-mediated prediabetes or type 2 diabetes mellitus (Figure copied with permission from Ref. [7]).

ingested carbohydrates in food) leads to increased pancreatic insulin secretion into the circulation that binds to body tissue insulin receptors (IR). Activation of IR tyrosine kinases phosphorylates IRS, which facilitates the PI3K/AKT intracellular pathway. Among the effects of the PI3K/AKT pathway include translocation of glucose transporters (GLUT4) located in muscle and adipose tissue from intracellular storage to the cell surface (i.e., plasma membrane), which then facilitates cellular glucose uptake, and reduced circulating glucose blood levels (See Fig. 2).

2.1.18. *Phosphorylation*

Phosphorylation is the addition of a phosphoryl group to a molecule that results in modulation of enzyme activity (activation or suppression) (See Fig. 2).

2.1.19. *Tumor necrosis factor (TNF)*

Tumor necrosis factor (TNF) was previously known as cachexin or TNF alpha) and is a cytokine that may promote insulin resistance. While adipocytes can produce TNF, the stromovascular fraction inflammatory cells produce the majority of TNF (See Fig. 3).

2.2. *Inflammation*

Adipose tissue is a highly active endocrine and immune organ that produces numerous factors influencing adipogenesis, fatty acid metabolism (i.e., lipogenesis and lipolysis), extracellular matrix maintenance, and angiogenesis (See Fig. 4).

Regarding endocrine function, adipocytes have cellular receptors for traditional hormones, nuclear receptors for other hormones, receptors for

cytokines or adipokines, receptors for neuronal hormones, as well as receptors for adenosine, lipoproteins (high density lipoproteins, low density lipoproteins, very low density lipoproteins), neuropeptide Y1 and Y5, prostaglandins, vascular endothelial growth factor and endocannabinoids [73]. These adipose tissue endocrine receptors help to regulate appetite and energy balance, adipogenesis, angiogenesis, vascular homeostasis (i.e., endothelial function) energy storage, nutrient transport, glucose homeostasis (i.e., insulin sensitivity), lipid metabolism, and blood pressure (See Fig. 6).

Regarding the immune system, depending on environment and circumstance, adipose tissue may release pro-inflammatory factors with cytokine activity, acute phase response proteins, proteins of the alternative complement system, chemotactic/chemoattractants for immune cells, and eicosanoids/prostaglandins, as well as anti-inflammatory factors [73]. Increased proinflammatory responses coupled with decreased anti-inflammatory responses from dysfunctional adipose tissue may contribute to insulin resistance, substantially due to the susceptibility of non-adipose tissues to the systemic effects of adiposopathy (i.e., increased circulatory immunopathies, endocrinopathies, and free fatty acids) (See Figs. 4 and 5).

2.2.1. *Adipose tissue macrophages (ATM)*

Most of the mass of adipose tissue is composed of lipid-laden mature adipocytes. Surrounding adipocytes in adipose tissue is the cellular stromal vascular fraction (SVF), which is composed of collagen matrix, preadipocytes, mesenchymal stem cells, fibroblasts, pericytes, endothelial cells, smooth muscle cells, blood/lymph vessels, nerve cells, and inflammatory cells (e.g., macrophages and T-cells) [74]. Due to the presence of mesenchymal progenitor cells, the SVF is a source of stem cell therapy, often harvested from adipose tissue via liposuction [75].

The adipocyte hypertrophy that often occurs with obesity may result in absolute or relative adipocyte hypoxia, adipocyte cell death, adipocyte cellular stress, fatty acid flux dysregulation, and release of adipocytokines that attract (i.e., via chemokines) and activate pro-inflammatory macrophages within the SVF [7,8,32,33,76,77]. Notable chemokines produced by adipose tissue include monocyte chemoattractant protein-1 which recruits immune cells, such as monocytes originally produced by the bone marrow, that differentiate locally in adipose tissue into macrophages (See Fig. 5). Notable adipokines produced by adipose tissue include tumor necrosis factor, leptin, adiponectin, and interleukin 6.

Relative to adipose tissue neutrophils, T and B lymphocytes, mast cells, and eosinophils [78], the most common leukocytes in adipose tissue stroma are macrophages, which are derived from the infiltration and differentiation of monocytes [76]. SVF inflammatory cells have been historically described as M1 vs M2 macrophages. According to this model, M1 macrophages increase with obesity and disproportionately secrete pro-inflammatory factors such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and monocyte chemoattractant protein–1 (MCP-1) [76,77]. In contrast, M2 macrophages predominate in lean individuals and disproportionately secrete anti-inflammatory factors such as interleukin-10 (IL-10) and transforming growth factor beta 1 (TGF-beta) [76,77]. With obesity, M1 macrophages increase, with the M1/M2 proportion "polarized" to a pro-inflammatory profile [76]. An updated model suggests that macrophage phenotypes represent a spectrum of functional diversity, with varied pro-inflammatory and anti-inflammatory effects upon T-cell activation, adipocyte progenitor activation, fibrosis, extracellular matrix regulation, adipocyte insulin sensitivity, and lipolysis regulation [79,80]. Irrespective of the model, adiposopathic signaling with obesity may cause adipose tissue macrophages to secrete proinflammatory cytokines that promote insulin resistance in adipose tissue, muscle, and liver (See Fig. 3).

2.2.2. *Monocyte chemoattractant protein-1*

Adipocyte hypertrophy associated with obesity can result in (relative) hypoxia, lipotoxicity, maladaptive mechanotransduction, mitochondrial/endoplasmic reticulum stress, and oxidative stress [81,82]. (See Fig. 3) The body may respond to these cellular insults via pathways mediated by JNK and adipokines [81], (See Fig. 5) both which promote

Table 2
Illustrative resources in Obesity Pillars applicable to diagnosis and treatment of obesity. A comprehensive discussion of the global management of patients with overweight/pre-obesity and obesity, as well as prediabetes and type 2 diabetes mellitus is beyond the scope of this Clinical Practice Statement. The Obesity Medicine Association (OMA) has published several guides towards specific aspects of obesity management.

Category	Title	Reference
Diagnosis	Obesity definition, diagnosis, bias, standard operating procedures (SOPs), and telehealth: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022	[2]
	Obesity history, physical exam, laboratory, body composition, and energy expenditure: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022	[111]
	Thirty Obesity Myths, Misunderstandings, and/or Oversimplifications: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022	[3]
	Obesity Pillars Roundtable: Body mass index and body composition in Black and Female individuals. Race-relevant or racist? Sex-relevant or sexist?	[14]
Nutrition & Physical Activity	Nutrition and physical activity: An Obesity Medicine Association (OMA) Clinical Practice Statement 2022	[112]
	Obesity pillars roundtable: Obesity and individuals from the Mediterranean region and Middle East	[113]
Behavior modification	Behavior, motivational interviewing, eating disorders, and obesity management technologies: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022	[114]
	Stress, psychiatric disease, and obesity: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022	[82]
Treatment	Anti-Obesity Medications and Investigational Agents: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022	[20]
	Obesity pillars roundtable: Phentermine – Past, present, and future	[115]
	Concomitant medications, functional foods, and supplements: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022	[116]
	Weight-centric treatment of type 2 diabetes mellitus	[117]
	Bariatric surgery, gastrointestinal hormones, and the microbiome: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022	[118]
Pediatrics	Assessment, differential diagnosis, and initial clinical evaluation of the pediatric patient with obesity: An Obesity Medical Association (OMA) Clinical Practice Statement 2022	[119]
	Social consequences and genetics for the child with overweight and obesity: An obesity medicine association (OMA) clinical practice statement 2022	[120]
	Nutritional and activity recommendations for the child with normal weight, overweight, and obesity with consideration of food insecurity: An Obesity Medical Association (OMA) Clinical Practice Statement 2022	[121]
	Metabolic, behavioral health, and disordered eating comorbidities associated with obesity in pediatric patients: An Obesity Medical Association (OMA) Clinical Practice Statement 2022	[122]
	Obesity Pillars roundtable: Metabolic and bariatric surgery in children and adolescents	[123]

Fig. 10. Basic healthful nutrition principles [112,113]. Dietary principles that apply to patients with obesity without diabetes mellitus are similar to nutritional recommendations for patients with obesity and type 2 diabetes mellitus (T2DM), as well as similar to nutritional interventions for patients with other potential adiposopathic conditions such as high blood pressure, dyslipidemia, and/or cardiovascular disease and cancer. Prescriptive dietary recommendations should be evidenced-based [3] and be healthful both qualitatively and quantitatively. Nutritional recommendation should be sufficiently patient-centered and culturally sensitive as to facilitate patient agreement and adherence [113,124–126]. In general, patients should avoid ultra-processed, high energy-dense foods, limit sodium, alcohol, and simple carbohydrates. Conversely, it is generally more healthful to prioritize whole foods that are high in fiber and micronutrients (e.g., whole fruits and vegetables). Especially in patients with diabetes mellitus, complex carbohydrates are preferred over simple carbohydrates, which often have a higher glycemic index/load.

* Many natural foods contain varying amounts of saturated, polyunsaturated, and monounsaturated fat. The data regarding the relationship of saturated fat-containing dairy products and cardiovascular disease is inconsistent and may be related to the size of the component fatty acids (i.e., number of carbons). Dairy food intake is often a component of "healthful" diets, such as the Mediterranean Diet. Additionally, most studies supporting saturated fats as unhealthful (e.g., especially regarding increased cardiovascular disease risk) evaluated isocaloric substitution for other nutrients as opposed to health effects of different types of saturated fats during clinically meaningful weight reduction. Weight reduction via carbohydrate restricted nutritional intervention in patients with pre-obesity or obesity, and pre-diabetes or T2DM, may contribute to improvement or remission in diabetes mellitus, reduction in high blood pressure, and improvement in blood lipids such as triglycerides and high-density lipoprotein cholesterol. That said, patients with genetic dyslipidemias, or patients with increased intestinal cholesterol absorption with weight reduction, may experience moderate to marked increases in low-density lipoprotein cholesterol with carbohydrate restriction, which if excessive or uncontrolled, may suggest the need to replace saturated fats with poly or monounsaturated fats and restrict dietary intake of dietary cholesterol, or perhaps consider medications such as cholesterol absorption inhibitors (e.g., ezetimibe) or statins [112].

insulin resistance and promote macrophage infiltration of adipose tissue. Monocyte chemoattractant protein-1 (MCP-1) is a chemokine [76] secreted by adipocytes in response to the increased adipocyte size and cellular insults. Unlike some other adipose tissue-produced cytokines, (e.g., TNF and IL-6), which mainly originate in adipose tissue macrophages, the initial basal release of MCP-1 is predominantly from

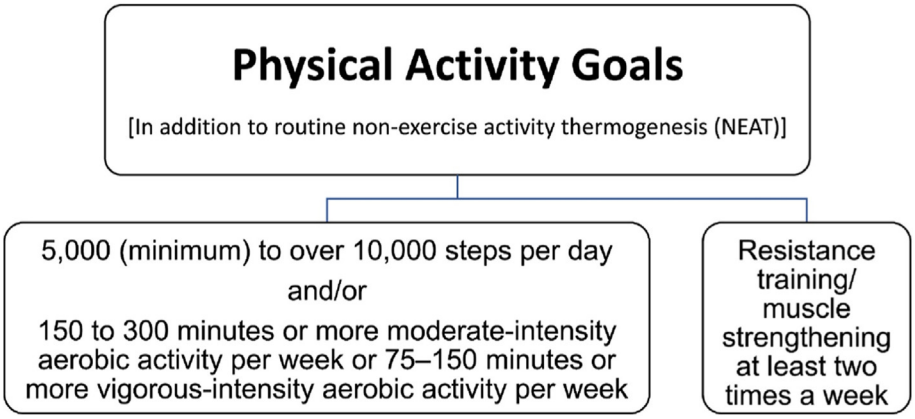

Fig. 11. Obesity Medicine Association (OMA) physical activity [112] recommendations. The OMA physical activity recommendations may differ from other physical activity recommendations by explicitly including daily steps as an acceptable goal for dynamic/aerobic physical activity. Averaging around 5000 steps per day may be a good starting point for many patients with obesity who have limited mobility, or who were previously physically inactive. Evidence supports that 5000 steps or more per day may reduce mortality compared to 2700 steps per day [127]. Among those who engage in over 10,000 steps per day, the risk of incident type 2 diabetes mellitus (T2DM) is substantially reduced [128]. The health benefits of increasing steps per day appear to be linear up to 10,000 steps per day, with each 2000-step increment above inactivity associated with 6% lower risk of progression toward T2DM [129]. Similarly, especially among those ≥60 years of age, the reduction in risk for cardiovascular disease events is generally linear from minimal to 7000/10,000 steps per day [130]. It is unclear that step intensity is associated with mortality after adjusting for total steps per day [131].

adipocytes [83]. The increase in monocyte recruitment to adipose tissue stroma and subsequent differentiation and polarization of monocytes to proinflammatory macrophages (i.e., immune cells that release pro-inflammatory cytokines) worsens insulin resistance [6,8,76]. A pro-inflammatory pathogenic cycle is created when initial adipocyte hypertrophy leads to hypoxia, lipotoxicity, altered mechanotransduction, cellular stress, inflammatory cytokine release (e.g., tumor necrosis factor), secretion of MCP-1, and recruitment of pro-inflammatory adipose tissue macrophages (See Fig. 5). These pro-inflammatory adipose tissue macrophages also secrete MCP-1, recruiting more proinflammatory macrophages to adipose tissue that release even more disruptive cytokines that are not only pathogenic, but may also stimulate adipocytes to produce even more MCP-1 – all leading to increased inflammation, insulin resistance, prediabetes, and possibly T2DM [81,83].

2.2.3. *Tumor necrosis factor (TNF)*

TNF is a pro-inflammatory cytokine primarily secreted by body macrophages, including adipose tissue stromal immune cells. Some TNF may be produced by adipocytes [76,84]. TNF secretion by adipocytes and adipose tissue macrophages may increase with obesity [76,84,85]. The physiologic effects of TNF include decreased peroxisome proliferator-activated receptor (PPAR) gamma activity and decreased adipose tissue functionality [via decreased (relative) adipocyte number and decreased adipocyte differentiation and increased adipocyte apoptosis]. TNF also decreases adipocyte lipid droplet-associated perilipin (i.e., a protein that normally inhibits lipolysis); thus allowing for hormone sensitive lipase to act on the lipid droplet for lipolysis, resulting in increased adipocyte lipolysis with increased circulating free fatty acids delivery to liver, muscle, and pancreas [76,84]. Along with glucolipotoxicity, inflammation such as via increased adiposopathic TNF, can impair pancreatic beta cell function and promote beta cell apoptosis [86]. Most applicable to this discussion is that TNF may promote mitochondrial dysfunction (increasing reactive oxygen species), decrease tyrosine kinase activation of IRS, increase inhibitory JNK-promoted serine phosphorylation of IRS, decrease insulin receptor activity, and decrease active glucose transporters (GLUT) [8,76,84,84], all contributing to post-insulin receptor resistance to insulin (See Figs. 2 and 3).

2.2.4. *Interleukins*

Obesity may increase interleukin-6 (IL-6), which can function as a pro-inflammatory cytokine secreted by "sick" adipose tissue, mainly adipose tissue stromal cells such as macrophages, but also adipocytes [5,6,76]. About one third of circulating IL-6 originates from adipocytes [6]. IL-6 induces hepatic C-reactive protein (CRP) production, helping to account for the increase in CRP found in patients with obesity and T2DM [87]. IL-6 may promote insulin resistance by impairing the tyrosine phosphorylation of insulin receptor and insulin receptor substrate [88] (See Fig. 3).

2.2.5. *Leptin*

Leptin is a hormone predominantly secreted by adipocytes, especially when adipocytes undergo hypertrophy [5,6,89]. Leptin acts on the hypothalamus to reduce appetite; however, its maximal effect appears to be at the upper range of normal [89]. The effects of obesity-promoted increased leptin levels are often insufficient to mitigate increased body fat, potentially because individuals with overweight or obesity may be susceptible to "leptin resistance" [89,90]. That said, it is more likely that the failure of physiologic, counter-regulatory mechanisms to prevent excessive body fat gain (e.g., release of leptin from hypertrophied adipocytes) is because other physiologic and environmental promoters of obesity overwhelm leptin's anti-obesity effects [82].

Increased leptin has a myriad of pathophysiologic effects regarding the neuroendocrine system, angiogenesis, oxidative stress, inflammation, fibrosis, platelet activation and aggregation, atherothrombosis, endothelial dysfunction, as well as cardiac remodeling and contractile function [91]. Leptin may have mixed effects on glucose metabolism. Leptin may decrease insulin secretion [5,6,89] and may contribute to insulin resistance. For example, chronic leptin stimulation of the arcuate nucleus of the hypothalamus may promote protein tyrosine phosphatase 1B (PTP1B), which inhibits insulin activity [92]. Increased leptin and insulin levels (along with postprandial effects) increase sympathetic nervous system activity, potentially contributing to insulin resistance [5,6,89] (See Fig. 3). Conversely, leptin may increase glucose tissue uptake by muscle and brown adipose tissue, decrease glucagon secretion by the pancreas, decrease corticosterone by the adrenal gland, decrease lipolysis in white adipocytes, and decrease gluconeogenesis and glucose output by the liver [5,6,89].

2.2.6. *Adiponectin*

While the data is not always consistent, the adiposopathic effects of adipocyte hypertrophy may help account for reduced adiponectin levels [93], with adiponectin being an anti-inflammatory adipocytokine produced by adipocytes that has insulin sensitizing effects [5,6,76]. Once attached to its cellular receptor, adiponectin stimulates production of 5' adenosine monophosphate-activated protein kinase (AMPK), which

Fig. 12. Summary of resistance training recommendations for patients with obesity [14,112]. The #1 priority in resistance training is primum non nocere ("first do no harm"), which is best achieved by a pre-physical-exercise health assessment (e.g., cardiovascular, pulmonary, musculoskeletal, and neurologic body systems) and patient education on safe resistance training techniques. Further, it is often advantageous to focus on the basic principles of this figure, with the use of an individual physical exercise prescription, rather than pursue a "quick fix" strategy via unproven and potentially interventions such as unsafe training practices and use of unproven supplements. Resistance training progress may best include muscle tape measurements and body composition, as opposed to body weight or the amount of weight lifted. Among the more efficient ways to increase total muscle mass is to train large muscle groups. Healthy posture, balance stabilization, back muscle strength, and endurance might best be achieved with physical exercise directed at developing "core" muscles. In most cases, both low load training (i.e., lower weights per set with more repetitions) and high load training (i.e., heavier weights with fewer repetitions) resistance will promote muscle fiber hypertrophy. In either case, muscle hypertrophy mainly occurs with sufficient effort that results in muscle overload. That said, just as with dynamic/aerobic training, what may matter most is adhering to a routine. For most individuals, adequate protein intake for muscle development can be achieved with healthful nutrition via natural food sources. Healthful sleep can favorably affect multiple body processes [132], including the effectiveness of resistance training; resistance physical exercise may in turn, improve sleep quality. Finally, resistance training should be considered as complementary to (and not a substitute for) dynamic/aerobic exercise training.

mediates cellular energy homeostasis [76]. AMPK promotes fatty acid oxidation, vasodilation, and cytoprotection [7,76]. Signals from the activated adiponectin receptor also activate IRS, which helps facilitate glucose uptake [5,6,76]. Decreases in anti-inflammatory cytokine production may be the result of adiposopathic increase in pro-inflammatory cytokine production (e.g., increased TNF downregulates adiponectin expression) [5,6,76] (See Fig. 3).

2.3. *Endocrinopathies*

Many adipokines have both inflammatory properties and endocrine functions (See Figs. 4–6). Thus, the mechanisms by which adipokines contribute to insulin resistance often reflects integrative inflammatory and endocrine pathogenic effects. Specifically, once bound to their target receptors, adipokines may act as classic hormones affecting the metabolism of tissues and organs [94].

Fig. 13. Optimal anti-obesity medications. Several factors determine the choice of optimal anti-obesity medications, which is best determined by developing an individualized plan based upon the patient's specific needs. While weight reduction as little as 5% among patients with obesity may improve metabolic parameters, clinical outcome benefits are best achieved by 15% weight reduction or more, which can be achieved by highly effective anti-obesity medications (heAOM) [31].

Beyond adipokines, an illustrative example of another endocrinopathy that may represent a model for how adiposopathic endocrinopathies contribute to insulin resistance involves the relationship of obesity to 11 beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1). 11β-HSD1is an enzyme produced in adipose tissue (and liver) that converts inactive cortisone to active cortisol and is increased with obesity ("local Cushing's syndrome") [95]. Increased 11β-HSD1 activity may amplify local glucocorticoid effects, even as circulating glucocorticoid levels are not elevated [96]. Adiposopathic increases in local tissue cortisol activity via increased 11β-HSD1 may increase lipolysis, increase lipotoxic release of free fatty acids, increase gluconeogenesis in the liver, and decrease glucose uptake in muscle [95].

Adipocyte hypertrophy is associated with increased expression levels of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). In addition to adiposopathic increase in pro-inflammatory cytokine production, increased 11β-HSD1 expression is another potential mechanism underlying reduced adiponectin synthesis in hypertrophic adipocytes [97]. Given that excessive glucocorticoid activity can contribute to metabolic diseases such as T2DM, hypertension, and cardiovascular diseases, 11β-HSD1 inhibition may be a target for pharmacotherapy of multiple obesity-related metabolic diseases [67].

2.4. Lipotoxicity, obesity, adiposopathy, insulin resistance, prediabetes, and type 2 diabetes mellitus

The metabolic disease complications of obesity are mostly the net result of how body organs respond to adiposopathic immunopathies and endocrinopathies [4] (Fig. 7). An often cited example is that during positive caloric balance and obesity, impaired uptake of energy in "sick" adipose tissue leads to increased circulating free fatty acids, and "ectopic" and pathogenic deposition of fatty acids and fats in various body locations and organs (See Fig. 8) [5–8,32,33,106]. Examples of adiposopathic ectopic fat deposition incudes visceral, pericardial, and perivascular adipose tissue, as well as fat deposition within and/or around liver, muscle, heart, pancreas, and kidney. In liver and muscle, increased circulating free fatty acids (FFA) lead to an increase in intracellular binding of free fatty acids to sphingolipids forming "toxic" ceramides and its metabolites [106,107] resulting in:

- Mitochondrial dysfunction
- Endoplasmic reticulum "stress"
- Impaired insulin receptor function
- Impaired glucose transporter expression (GLUT2 for liver, GLUT4 for muscle and adipose tissue)

In liver, intrahepatic triglycerides are inert and do not appear to directly impair insulin action. However, the intrahepatic influx of free fatty acids from circulation and the metabolic processes leading to triglyceride formation is often accompanied by the formation of metabolically bioactive lipids, namely ceramides and diacylglycerols that can cause insulin resistance by inhibiting insulin signaling by impairing tyrosine phosphorylation of insulin receptor substrate, phosphoinositide-3-kinase, protein kinase C-theta, and protein kinase B (also known as AKT) [4] (See Figs. 2 and 3).

In skeletal muscle, and during basal conditions, free fatty acids serve as the primarily fuel. After glucose or mixed-meal ingestion, increased pancreatic insulin into the circulation suppresses the lipolysis of adipose tissue triglycerides, decreases circulating free fatty acid levels, and

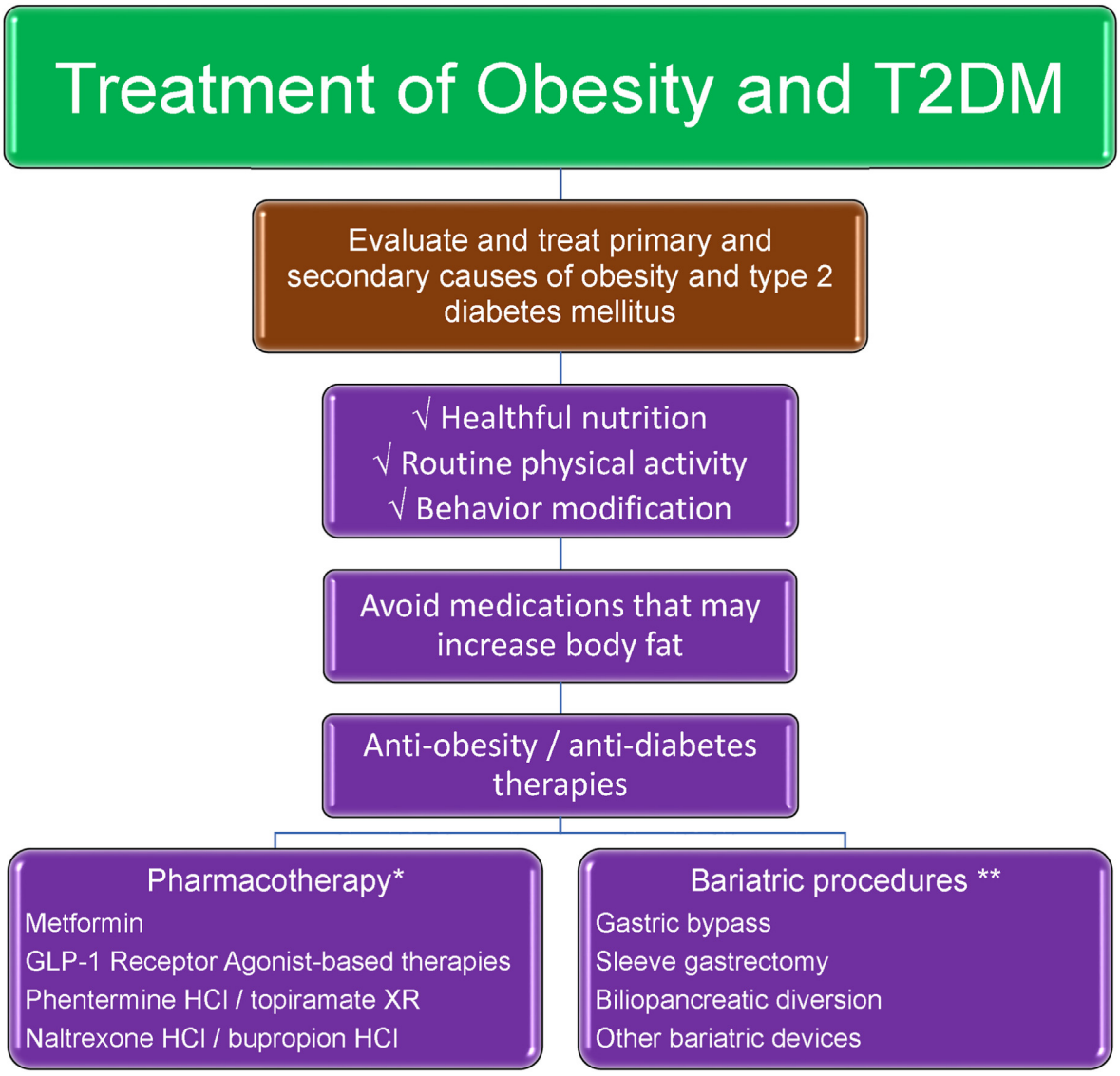

Fig. 14. Treatment of patients with obesity and type 2 diabetes mellitus (T2DM). Determining optimal therapy begins with diagnosing and treating the causes of the diseases of obesity and T2DM. Healthful nutrition, routine physical activity, and behavioral therapy are recommended to achieve and maintain ≥5% weight reduction for most patients with T2DM and pre-obesity/overweight or obesity. Additional weight reduction often results in further improvements in glycemic control and reducing cardiovascular disease (CVD) risk factors, and potentially a reduction in CVD event risk [15,133–135]. Factors that determine the optimal choice of anti-obesity/anti-diabetes medications in patients with pre-obesity/overweight or obesity include safety, efficacy, effects on body weight, effect on blood glucose, effect on potential diabetes remission, improvement in cardiovascular disease (CVD) risk factors, and evidence of reduced CVD outcomes [133].

* Most participants in the cardiovascular outcomes trials of anti-diabetes medications proven to reduce CVD risk included patients treated with baseline metformin. However, organizations such as the American Diabetes Association (ADA), have recommended metformin as an optional concurrent treatment to reduce CVD risk [136]. Metformin has limited data supporting beneficial CVD outcomes [137], and the glucose lowering effects of metformin may wane over time, with among the greatest predictors of metformin failure being higher levels of baseline hemoglobin A1c [138]. Among patients at CVD risk, the ADA gives preference to anti-diabetes therapies with proven CVD benefits, such as glucagon like peptide – 1 receptor agonist (GLP-1 RA) and sodium glucose transporter 2 inhibitors (SGLT2i) [136]. GLP- 1 RA – based anti-diabetes therapies with cardiovascular outcomes trials supporting reduction in major adverse cardiovascular events (MACE) include liraglutide, semaglutide, dulaglutide, and efpeglenatide. Tirzepatide is a GLP-1 RA and glucose-dependent insulinotropic polypeptide that improves multiple CVD risk factors and that is currently undergoing CVD outcomes trials [139,140]. SGLT2i with proven CV benefits are also recommended; however, SGLT2i promote only mild weight reduction and no SGLT2i is indicated to treat obesity [15,134,135]. Data are lacking regarding long-term, prospective, randomized, clinical efficacy and safety of phentermine monotherapy for glycemic control and CVD risk. Many patients with obesity are at high risk for CVD. T2DM is a major cardiovascular disease risk factor. Phentermine is contraindicated in patients with CVD [115].

** Metabolic/bariatric surgery [118] can improve glucose control in patients with T2DM and obesity, and may also promote remission of T2DM [133,141].

stimulates muscle glucose uptake via insulin-stimulated GLUT 4 – thus switching the predominant muscle fuel from fatty acids to glucose [4] (See Fig. 2). After entering the myocyte, glucose is phosphorylated and oxidized for fuel via glycolysis or stored as non-oxidative glycogen. Individuals with obesity and/or type 2 diabetes often have a "lipotoxic" impairment of the insulin receptor (See Figs. 2 and 3) [4].

Regarding pancreatic beta cells, over exposure to glucose due to hyperglycemia [108] and exposure to certain lipids derived from increased circulating free fatty acids may reduce insulin secretion due to *gluco*-lipotoxicity [107,109]. Increased sphingolipid (e.g., ceramide) formation promotes pancreatic beta cell apoptosis [107,109]. Control of glucose levels and a reduction in liver and pancreas fat content with weight loss in patients with overweight/obesity may allow recovery of beta cell function, especially among patients with shorter duration of T2DM [110].

In short, the degree that obesity-mediated immune, endocrine, free fatty acid, and other signaling adversely affects metabolic health depends on how multiple body organs navigate these adiposopathic offensives, via crosstalk and interactions, as well as biologic reactions and responses that may be unique to the individual (See Fig. 9).

3. Etiology, diagnosis, and treatment

A comprehensive discussion of the diagnosis and treatment of obesity is beyond the scope of this review focused on pre-obesity/obesity and pre-diabetes/T2DM (see Fig. 8). Many of the principles in the diagnosis and treatment of patients with obesity and diabetes similarly apply to patients with obesity alone. Table 2 provides some Obesity Pillars publications relevant resources to the diagnosis, management, and treatment

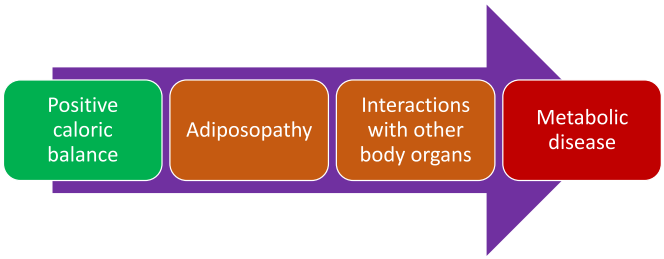

Fig. 15a. Adipocentric paradigm.

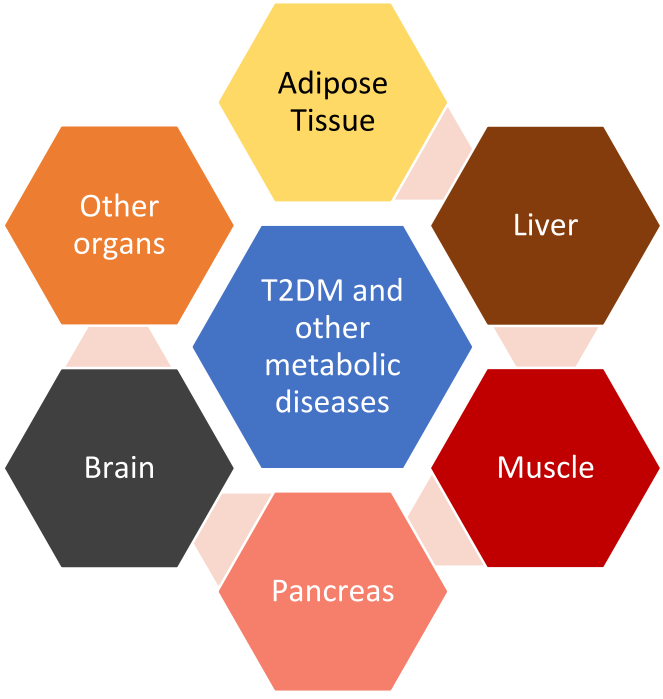

Fig. 15b. Discordant multiorgan interaction paradigm.

Fig. 15a and b: Paradigm perspectives regarding the primary cause of common obesity-related metabolic diseases such as type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia

Major risk factors for T2DM include increased body fat, age ≥45, physical inactivity, and genetics (family history and race). Not all cases of common metabolic diseases are attributable to increased body fat [3]. For example, some cases of T2DM can be caused by rare conditions such as hemochromatosis, hypercortisolism, excessive growth hormone, pancreatic insufficiency, side effects of concomitant therapies, genetic syndromes of insulin resistance, and genetic syndromes of limited pancreatic insulin secretion [3]. No matter the paradigm, T2DM is most often due to discordant multiorgan interactions (See Fig. 15b), and not just an increase in body fat. In fact, T2DM can sometimes be due to reduced body fat (not increased body fat), as occurs with lipodystrophy [156]. This line of thinking may potentially lead to the dubious conclusion that caloric intake, adipocyte hypertrophy, adipose tissue accumulation, and adipose tissue dysfunction (e.g., endocrinopathies or immunopathies) are irrelevant to the pathogenesis of most cases of cardiometabolic diseases such as T2DM [3]. However, the clinical data supports that obesity and adiposopathy are the most common modifiable factors when assessing the cause and treatment of metabolic diseases such as T2DM. Because even when remission of T2DM is correlated with a reduction in excess fat from the liver and pancreas [157], this is usually within the context of substantial weight reduction [158]. Furthermore, among those with obesity, the origin of free fatty acids delivered to the liver in the postabsorptive state is usually about 20% from lipolysis from visceral fat (although as high as 50% in some individuals), and 80% from lipolysis of subcutaneous adipose tissue [4]. The origin of most systemic free fatty acids delivered to muscle is from subcutaneous adipose tissue, and not visceral adipose tissue (which is drained into the liver via the portal circulation) [159]. Thus, both subcutaneous and visceral adipose tissue play a role in fatty liver, fatty muscle, and thus play a central role in insulin resistance and T2DM. Weight reduction via hypocaloric diets result in reduction in subcutaneous adipose tissue, visceral adipose tissue, pancreatic fat, and liver fat, with the reduction of liver lipid content being the strongest predictor of insulin resistance improvement after weight reduction [160], likely because a reduction in intraorgan fat (i.e., hepatic fat) and reduction in ectopic fat (i.e., visceral fat) are both markers for improved adipose tissue function. In summary, increased body fat is the most consistent potentially modifiable risk factor leading to pre-diabetes/T2DM and many other metabolic diseases (e.g., high blood pressure and adiposopathic dyslipidemia) [9]. Risk factors such as age, race, genetic sex, other genetic inheritance, and concurrent illnesses (e.g., some neurological, metabolic, and body organ disorders) are not modifiable [3]. Conversely, body fat is often modifiable. Utilizing the principles of Ockham's razor (i.e., parsimony, economy, or succinctness in problem-solving) with the patient-centered provision that reversibility is preferred over irreversibility when assigning causation, then a logical conclusion might be: "When multiple abnormalities promote an adverse health outcome, it is the defect most directly, simply, and reversibly associated with promoting a disease, and the defect most beneficial when corrected, which is best labeled the 'primary cause'" [9] The adipocentric paradigm and philosophical perspective regarding causality of common cardiometabolic diseases and cancer helps explain why body fat gain is often accompanied by onset of cardiometabolic disease (i.e., development of adiposopathic "sick fat") [2]. The adipocentric paradigm helps explain why healthful nutrition, routine physical activity, behavior modification, anti-obesity medication and bariatric procedures may not only reduce body weight, may not only improve metabolic diseases and cardiometabolic risk factors, but also improve cardiometabolic disease and in some cases improve cancer outcomes [2,20,44,112,114,118]. The adipocentric paradigm is a model that best supports the implementation of the four pillars of obesity management (e.g., nutrition, physical activity, behavior modification, and anti-obesity medications), as well as helps support the rationale for bariatric procedures in patients with overweight or obesity. A central focus on managing body fat in the treatment of obesity and its complications is supported by the potential remission of metabolic diseases (See Fig. 16) and provides rationale why pre-obesity/obesity may often be considered the most clinically relevant treatment target and priority for patients without adverse acute complications (See Fig. 17) (see Fig. 18).

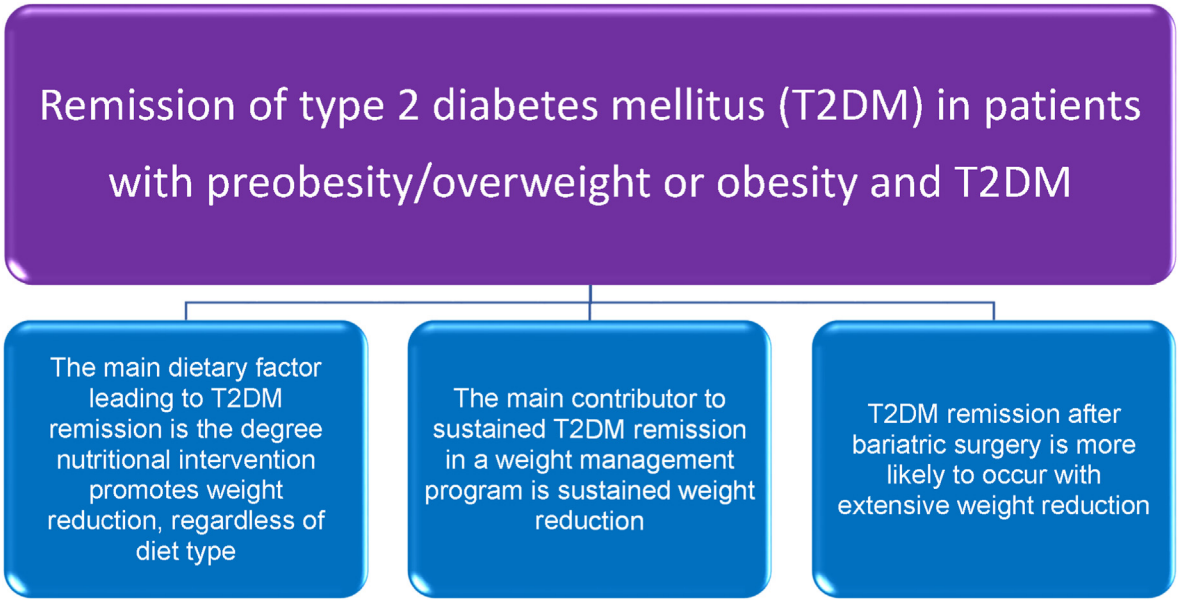

Fig. 16. Intervention principles regarding remission of type 2 diabetes mellitus (T2DM) [161]. Strong and consistent evidence supports obesity management as delaying the progression from prediabetes to type 2 diabetes, improving glycemia in patients with T2DM, reducing the need for glucose-lowering medications, and promoting sustained diabetes remission through at least 2 years [133]. Modest weight reduction (i.e., 3–7% of baseline weight) improves glycemia and other intermediate cardiovascular risk factors while larger sustained weight losses (i.e., >10%) often results in disease-modifying effects such as possible remission of type 2 diabetes (and weight reduction ≥15% might best reduce cardiovascular disease outcomes and mortality) [133]. If intermittent fasting results in weight reduction, then this may also enhance remission of T2DM [162] Predictors of remission of T2DM include shorter duration of T2DM (<2 years duration), fewer number of anti-diabetes medications required to achieve euglycemia, and clinically meaningful weight reduction [161,163]. Among those with obesity, the most effective approach to prevent the progression of prediabetes to diabetes mellitus is clinically meaningful weight reduction [164]. The main dietary contributor to diabetes remission is weight reduction (regardless of macronutrients) [133]. While very low energy diets and formula meal replacement appear the most effective approaches, low carbohydrate diets and their affiliated weight reduction may be more effective in T2DM remission at 6 months, compared to low fat diets [165]. In an open-label, cluster-randomized controlled trial conducted at primary care practices, the main contributor to sustained T2DM remission in a structured weight management program was sustained weight reduction [166], with remission correlated with the amount of weight reduction (i.e., up to 86% remission among participants who lost 15 kg or more) [4]. In a national health record review in England, greater T2DM remission rates were consistently associated with weight loss and degree of weight loss [167]. A meta-analysis supports that patients with extensive weight loss were more likely to achieve T2DM remission after bariatric surgery [168], with the caveat that diabetes remission with bariatric surgery may be achieved via mechanisms beyond weight reduction alone [118,169]. Also, consistent with principle that the health benefits of body fat weight reduction depends on promoting favorable health effects upon adipose tissue function, the simple surgical removal of functional body fat may not result in metabolic health benefits (e.g., liposuction of subcutaneous abdominal adipose tissue or removal of intra-abdominal adipose tissue by omentectomy) [4]. Similarly, no approved or investigational medication exclusively developed to reduce hepatic fat in patients with nonalcoholic fatty liver disease (NAFLD) is approved to treat T2DM, much less promote T2DM remission (i.e., independent of weight reduction) [170]. Conversely, anti-obesity medications (e.g., glucagon-like peptide receptor agonists) may have beneficial effects on hepatic steatosis and inflammation in patients with NAFLD [171]. Overall: (a) body fat reduction must be induced by negative energy balance to achieve metabolic benefits [4], (b) clinically meaningful weight reduction and improvement in adipose tissue function can be achieved with reduced-caloric intake regardless of macronutrients [172], (c) the number of meals per day correlates better with weight change than timing of meals [173], (d) time-restrictive eating with caloric restriction produces no more weight reduction, body fat reduction, or improvement in metabolic risk factors than caloric restrictions alone [174], (e) with the possible exception of protein intake, evidence of relative differences between carbohydrates and fats in appetite regulation is either lacking or inconsistent [175,176], (f) isocaloric very low carbohydrate/high fat diets do not differ from high carbohydrate/low fat diets with regard to weight reduction (although low carbohydrate diets may reduce fasting and post prandial glucose and insulin concentrations) [177], and (g) weight reduction is the most consistent parameter in achieving remission of T2DM. These principles highlight the health importance of weight reduction among patients with obesity and T2DM. They help refute the myth that obesity (and its complications) are unrelated to the energy density and caloric intake of food [3]. Regarding macronutrients: "There may be health reasons to emphasize one macronutrient over another in a diet, but from the perspective of energy balance, total energy intake, rather than its source, is the critical factor to address [175]."

of obesity. Figs. 10–12 provide general principles regarding healthful nutrition and physical activity in treating obesity, with or without diabetes mellitus.

3.1. *Anti-obesity medications and type 2 diabetes medications*

Fig. 13 describes factors to consider when choosing the optimal anti-obesity medication. Fig. 14 describes anti-obesity therapies for treatment of patients with obesity and T2DM. Factors to consider in choosing optimal anti-obesity and anti-diabetes medications in patients with obesity and T2DM includes safety, efficacy, effects on body weight, effects on metabolic parameters and health outcomes (i.e., cardiovascular effects). Some anti-diabetes medications may increase body weight (e.g., sulfonylureas, meglitinides, many insulins, and PPAR gamma agonists) [116,117]. Other anti-diabetes medications are weight neutral (e.g., DPP-IV inhibitors). Some anti-diabetes medications may produce mild weight loss (e.g., metformin, alpha glucosidase inhibitors, SGLT2 inhibitors, and amylin mimetics) [116,117]. Finally, some anti-diabetes medications can produce clinically meaningful weight loss (such as GLP-1 – based therapies) [116,117], with some anti-diabetes agents approved as anti-obesity medications at doses higher than when used to treat T2DM. Table 3 shows cardiovascular outcome trial results of anti-diabetes medications [20]. Tirzepatide is a dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist evaluated in a series of clinical trials for treatment of type diabetes mellitus (SURPASS studies) and for treatment of obesity (SURMOUNT studies) [20]. Semaglutide is evaluated in a series of clinical trials for treatment of T2DM (PIONEER studies) and for treatment of

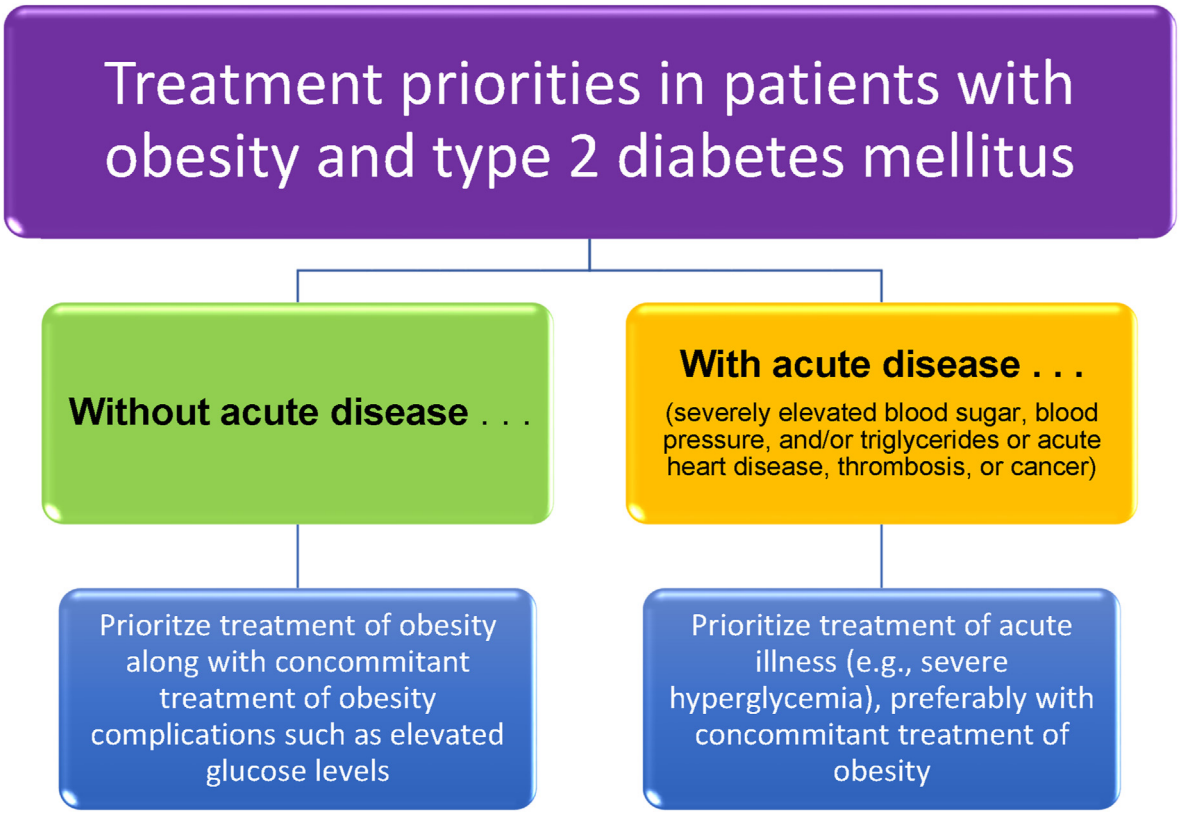

Fig. 17. "Treat obesity first" prioritization for patients with obesity and type 2 diabetes mellitus (T2DM) without acute disease. Treatment of obesity is the priority for most patients without acute illness, especially if the therapies chosen for treatment of the obesity are also expected to improve the complications of obesity. Conversely, patients with marked increases in glucose and/or blood pressure, severe dyslipidemia (e.g., severe hypertriglyceridemia), acute thrombosis, cardiovascular disease (CVD), or cancer should have these acute metabolic abnormalities urgently assessed, managed, and treated – preferably with concomitant interventions that may also improve obesity. For example, while glucagon-like peptide-1 receptor agonist based therapies may reduce body weight and improve glycemic control in patients with overweight/obesity [20], if the patient with obesity and T2DM has heart failure, then beyond their indicated use as anti-diabetes medications, some sodium glucose transporter 2 inhibitors (SGLT1i) have clinical outcome data to support improvement in both CVD and heart failure [178], and may also facilitate mild weight reduction [179,180].

Table 3
Illustrative cardiovascular disease outcomes studies in patients with diabetes mellitus since the 2008 FDA guidance. Shown are studies on CVD outcomes in patients with diabetes mellitus. Most study participants had preobesity/overweight or obesity [12,13,15,142–153]. CVD:cardiovascular disease; DPP-IV:dipeptidyl peptidase 4; MACE:major adverse cardiac events; PPAR:peroxisome proliferator activated receptor; SGLT-2:sodium-glucose cotransporter-2.

Drug Class	Trial	Drug	Primary Endpoint	N (Median Duration)	CVD outcomes
DPP-4 Inhibitors	SAVOR-TIMI 53	Saxagliptin	MACE	16,492 (2.1 years)	↔ (2013)
	EXAMINE	Alogliptin	MACE	5380 (1.5 years)	↔ (2013)
	TECOS	Sitagliptin	MACE	14,671 (3.0 years)	↔ (2015)
	CAROLINA	Linagliptin	MACE + UA	6000 (7.6 years)	Non-inferior to glimepiride (2019)
	CARMELINA	Linagliptin	MACE	6991 (2.2 years)	↔ (2018)
GLP-1 Receptor Agonists	ELIXA	Lixisenatide	MACE	6068 (2.1 years)	↔ (2015)
	LEADER	Liraglutide	MACE	9340 (3.8 years)	↓ (2016)
	SUSTAIN 6	Semaglutide (subcutaneous. Injection)	MACE	3297 (2.1 years)	↓ (2016)
	FREEDOM-CVO	Exenatide cont. release	MACE	>4000 (< 3 years)	↔ (2016)
	EXSCEL	Exenatide extended-release (QW)	MACE	14,752 (3.2 years)	↔ (2017)
	HARMONY	Albiglutide	MACE	9463 (1.6 years)	↓ (2018)
	PIONEER - 6	Semaglutide (oral)	MACE	3183 (1.3 years)	↔ (2019)
	REWIND	Dulaglutide	MACE	9622 (6.5 years)	↓ (2019)
	AMPLITUDE-O	Efpeglenatide	MACE	4076 (1.81 years)	↓ (2021)
SGLT2 Inhibitors	EMPA-REG OUTCOME	Empagliflozin	MACE	7020 (3.1 years)	↓ (2015)
	CANVAS	Canagliflozin	MACE	10,142 (2.4 years)	↓ (2017)
	DECLARE-TIMI-58	Dapagliflozin	MACE	17,160 (4.2 years)	↓ CV deaths/CHF hospitalization (2018)
	VERTIS - CV	Ertugliflozin	MACE	8246	↔ (2020; did reduce CHF)
Insulin	DEVOTE	Degludec	MACE	6509 (~2 years)	Non inferior to glargine (2017)
PPAR Gamma Agonists	IRIS	Pioglitazone p stroke/TIA	MACE	3895 (4.8 years)	↓ (2016)
Alpha Glucosidase Inhibitor	ACE trial (Chinese population in patients with glucose intolerance)	Acarbose	MACE	6522 (5.0)	↔ (2017)
	Taiwan population	Acarbose	MACE	14,306	↓ Compared to adding sulfonylurea to metformin (2018)

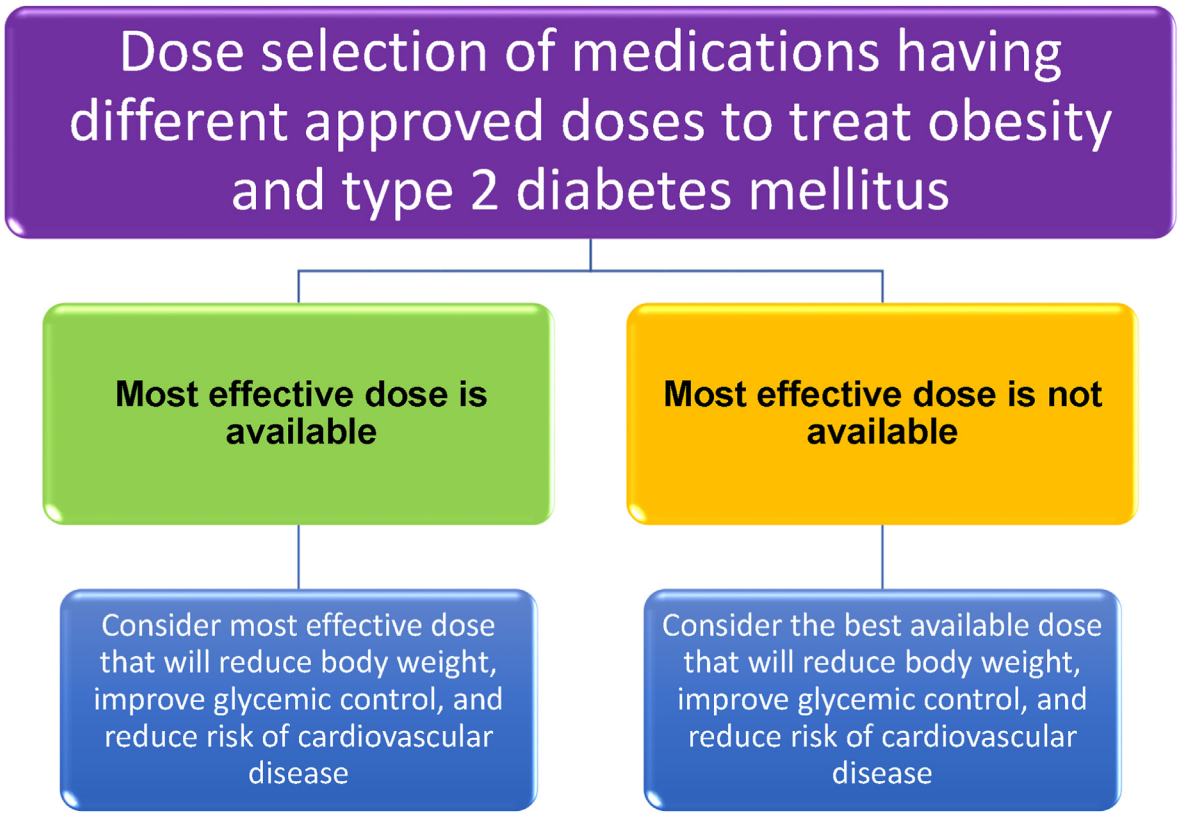

Fig. 18. "Best available dose" approach in choosing medications for patients with obesity and type 2 diabetes mellitus (T2DM). Some medications are indicated to treat both obesity and T2DM, but at different doses for each disease. For example, semaglutide is a glucagon-like peptide-1 receptor agonist that at lower injectable doses 0.25–2.0 mg per week is indicated to improve glycemic control in patients with T2DM while semaglutide at 2.4 mg subcutaneously per week is approved for chronic weight management of patients with overweight with weight-related complications or obesity [20]. Challenges arise when higher medication doses for obesity are not available, as may occur with supply limitations or prohibitive cost. In such cases, for patients with obesity and T2DM, if the medication has proven benefits in reducing body weight, improving glycemic control, and reducing cardiovascular disease risk, then the optimal medication dose choice would be the dose most available to the patient.

obesity (STEP or Semaglutide Treatment Effects in People with Obesity) [20] (See Table 4).

3.2. *Priority of treatment – "Treat obesity first"*

Fig. 15 describes the "treat obesity first" therapeutic paradigm (https://www.consultant360.com/exclusives/new-guidelines-pharmacological-management-obesity). If patients with obesity and diabetes mellitus have acute illnesses, such as marked hyperglycemia, uncontrolled high blood pressure, severe hypertriglyceridemia, cardiovascular disease, or cancer, then these acute medical disorders should be treated acutely. Otherwise, comprehensive treatment of obesity is the priority for most patients with obesity and T2DM, with optimal therapies providing clinically meaningful weight reduction and improvement in the complications of obesity – including improvement in glucose control. Fig. 16 describes how weight reduction is the most consistent factor that promotes remission of T2DM, irrespective of dietary macronutrients, clinical approach, or type of bariatric surgery. Finally, Fig. 18 provides an algorithmic, practical approach to anti-obesity and anti-diabetes medication dose selection, based upon the availability of medications that are approved as both anti-obesity and anti-diabetes medications, but at different doses.

4. Conclusions

This Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) is intended to provide clinicians an overview of the obesity-related cardiometabolic risk factor of diabetes mellitus. T2DM is a common complication of obesity, which occurs as the result of adverse immunologic, endocrinologic, and lipotoxic adipose tissue processes that contribute to insulin resistance and beta cell dysfunction. The determination as to whether these adiposopathic consequences ultimately lead to clinical metabolic disease substantially depends on the response of non-adipose tissue organs such as liver, muscle, pancreas, kidney, and brain. Many of the principles in the diagnosis and treatment of patients with obesity and diabetes similarly apply to patients with obesity alone. Preferred anti-obesity therapies for treatment of patients with obesity and T2DM include those that reduce body weight, improve glycose levels and other metabolic parameters, and improve health outcomes (i.e., cardiovascular disease). Several anti-diabetes mellitus medications have clinical trial evidence to support clinically meaningful weight reduction and improvement in cardiovascular disease outcomes. Ongoing clinical trials are evaluating the potential cardiovascular disease benefits of tirzepatide and semaglutide in patients with obesity but without diabetes mellitus. Given the numerous obesity "sick fat diseases" (i.e., adiposopathy) and "fat mass diseases," and given that most of the patients in T2DM cardiovascular outcomes trials had pre-obesity/obesity, then this supports the "treat obesity first" therapeutic paradigm. Patients with or without diabetes mellitus who have acute illnesses should have these illnesses treated acutely (e.g., marked hyperglycemia, uncontrolled high blood pressure, severe hypertriglyceridemia, cardiovascular disease, or cancer). However, beyond that, treatment of obesity is the priority for most patients with obesity and T2DM, with optimal therapies providing clinically meaningful weight reduction, therapeutic benefits and/or potential remission of the complications of obesity (i.e., T2DM), and

Table 4
Illustrative cardiovascular outcomes trials of therapeutic agents approved or potentially to be approved for treatment of both obesity and type diabetes mellitus.

Therapeutic agent	Metabolic parameter	Cardiovascular outcomes trials	Reference link
Tirzepatide	Obesity (Injectable SQ)	A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)	https://clinicaltrials.gov/ct2/show/NCT05556512
Tirzepatide	Type 2 Diabetes Mellitus (Injectable SQ)	A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT)	https://www.clinicaltrials.gov/ct2/show/NCT04255433
Semaglutide	Obesity (Injectable 2.4 mg SQ weekly)	Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT)	[20]
	Type 2 Diabetes Mellitus (Injectable 0.5 or 1.0 mg SQ weekly)	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6)	[154]
	Type 2 Diabetes Mellitus (Oral 3/7/14 mg per day)	Semaglutide Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes (SOUL)	[20]
Liraglutide	Type 2 Diabetes Mellitus (Injectable 1.8 mg SQ daily)	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)	[155]

improved disease outcomes (e.g., cardiovascular disease or cancer).

Transparency [181]

This manuscript was derived and edited from the 2021 Obesity Medicine Association (OMA) Obesity Algorithm. Beginning in 2013, OMA created and maintained an online Adult "Obesity Algorithm" (i.e., educational slides and eBook) that underwent yearly updates by OMA authors and was reviewed and approved annually by the OMA Board of Trustees. This was followed by a similar Pediatric "Obesity Algorithm," with updates approximately every two years by OMA authors. Authors of prior years' version of the Obesity Algorithm are included in Supplement #1.

Group composition

Over the years, the authors of the OMA Obesity Algorithm have represented a diverse range of clinicians, allied health professionals, clinical researchers, and academicians. (Supplement #1) The authors reflect a multidisciplinary and balanced group of experts in obesity science, patient evaluation, and clinical treatment.

Author contributions

HEB and the medical writer (see below) crafted the first draft. SB and TLC reviewed, edited, and approved the manuscript version before and after peer review.

Managing disclosures and dualities of interest

Potential dualities or conflicts of interest of the authors are listed in the Disclosures section. Assistance of a medical writer paid by the Obesity Medicine Association is noted in the Acknowledgements section. Neither the prior OMA Obesity Algorithms, nor the publishing of this Clinical Practice Statement received outside funding. The authors of prior OMA Obesity Algorithms never received payment for their writing, editing, and publishing work. Authors of this Clinical Practice Statement likewise received no payment for their writing, editing, and publishing work. While listed journal Editors received payment for their roles as Editors, they did not receive payment for their participation as authors.

Evidence

The content of the OMA Obesity Algorithm and this manuscript is supported by citations, which are listed in the References section.

Ethics review

This OMA Clinical Practice Statement manuscript was peer-reviewed and approved by the OMA Board of Trustee members prior to publication. Edits were made in response to reviewer comments and the final revised manuscript was approved by all the authors prior to publication. This submission did not involve human test subjects or volunteers.

Conclusions and recommendations

This Clinical Practice Statement is intended to be an educational tool that incorporates the current medical science and the clinical experiences of obesity specialists. The intent is to better facilitate and improve the clinical care and management of patients with pre-obesity and obesity. This Clinical Practice Statement should not be interpreted as "rules" and/or directives regarding the medical care of an individual patient. The decision regarding the optimal care of the patient with pre-obesity and obesity is best reliant upon a patient-centered approach, managed by the clinician tasked with directing an individual treatment plan that is in the best interest of the individual patient.

Updating

It is anticipated that sections of this Clinical Practice Statement may require future updates. The timing of such an update will depend on decisions made by Obesity Pillars Editorial team, with input from the OMA members and OMA Board of Trustees.

Disclaimer and limitations

Both the OMA Obesity Algorithms and this Clinical Practice Statement were developed to assist health care professionals in providing care for patients with pre-obesity and obesity based upon the best available evidence. In areas regarding inconclusive or insufficient scientific evidence, the authors used their professional judgment. This Clinical Practice Statement is intended to represent the state of obesity medicine at the time of publication. Thus, this Clinical Practice Statement is not a substitute for maintaining awareness of emerging new science. Finally, decisions by practitioners to apply the principles in this Clinical Practice Statement are best made by considering local resources, individual patient circumstances, patient agreement, and knowledge of federal, state, and local laws and guidance.

Diclosures

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Altimmune, Amgen, Anji Pharma, AstraZeneca, Axsome, BioHaven, Bionime, Boehringer Ingelheim, CinCor, CSL Behring, Eli Lilly, Esperion, Evidera, Gan and Lee, Home Access, Lexicon, Madrigal, Matinas, Merck, Metavant, New Amsterdam, Novartis, NovoNordisk, Pfizer, Regeneron, Sanofi, Satsuma, Selecta, TIMI, and Vivus. HEB has served as a consultant/advisor for 89Bio, Altimmune, Amgen, Boehringer Ingelheim, and Esperion, and speaker for Esperion.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.obpill.2023.100056.

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