Obesity and cardiovascular risk: a call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: part A: mechanisms of obesity induced hypertension, diabetes and dyslipidemia and practice guidelines for treatment

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Obesity is a key factor for cardiovascular diseases and complications. Obesity is associated with hypertension, dyslipidemia and type II diabetes, which are the major predictors of cardiovascular disease in the future. It predisposes for atrial fibrillation, heart failure, sudden cardiac death, renal disease and ischemic stroke that are the main causes of cardiovascular hospitalization and mortality. As obesity and the cardiovascular effects on the vessels and the heart start early in life, even from childhood, it is important for health policies to prevent obesity very early before the disease manifestation emerge. Key roles in the prevention are strategies to increase physical exercise, reduce body weight and to prevent or treat hypertension, lipids disorders and diabetes earlier and efficiently to prevent cardiovascular complications. Epidemiology and mechanisms of obesity-induced hypertension, diabetes and dyslipidemia will be reviewed and the role of lifestyle modification and treatment strategies in obesity will be updated and analyzed. The best treatment options for people with obesity, hypertension, diabetes and dyslipidemia will discussed.

Keywords: cardiovascular risk, diabetes, dyslipidemia, guidelines, hypertension, obesity

Abbreviations: β-blockers, beta blockers; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BP, blood pressure; CCBs, calcium channel blockers; CETP, cholesteryl ester transfer protein; CRF, cardiorespiratory fitness; CRP, C-reactive protein; DAG, diacylglyceride; DPP-IV, dipeptidyl peptidase-IV; FFAs, free-fatty acids; GLP1, glucagon-like peptide 1; HBA1c, hemoglobin A1c; HDL, high-density lipoprotein; IKK, IκB kinase; IL-1, interleukin-1β; IL-6, interleukin-6; JNK, c-JUN N-terminal kinase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; MCP-1, macrophage chemoattractant protein-1; NAFLD, nonalcoholic fatty liver disease; NF-Kb, nuclear factor-κB; NO, nitric oxide; OSA, obstructive sleep apnea; PCSK9, proprotein convertase subtilisin/kexin type 9; PPARγ, peroxisome proliferator-activated receptor gamma; PRA, plasma renin activity; RAS, renin–angiotensin system; SGLT2, sodium-glucose co-transporter 2; SNS, sympathetic nervous system; TNF-a, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VLDL, very low-density lipoprotein

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OBESITY AND HYPERTENSION

Epidemiology, mechanisms and pathophysiology

Obesity is an established risk factor for hypertension [1,2]. The prevalence of obesity increased in the United States at least in 1990–2005 [3]. These increases have occurred in children, adolescents and adults, in both sexes and all ethnic groups. Hypertension is more than twice as prevalent in obese compared with nonobese individuals [4]. Age-adjusted prevalence of hypertension increased from 24.4 to 28.9% between 1988–1994 and 1999–2004 in USA. The increase in BMI can account for this increased prevalence of hypertension in men, and for a large portion in women [5]. Abdominal obesity was found to be associated with a two to three-fold increased risk of hypertension in USA and European populations [6,7]. The relationship between BMI with mean 24-h daytime and night-time blood pressure (BP), pulse pressure and heart rate has been confirmed from large studies. The incidence of white-coat hypertension and true hypertension was also found to be higher in overweight and obese individuals compared with normal weight individuals. A higher incidence of nondipping status in obesity was also reported in adults and children [8–12].

The mechanisms by which obesity directly causes hypertension are still an area of intense research. Adipose tissue production of adipokines and cytokines, neurohumoral pathways, and metabolic functions contribute to mechanisms that cause hypertension (Fig. 1). Obesity-related hypertension may be the result of a combination or overlap of a number of these factors. Activation of the sympathetic nervous system (SNS), measured with direct or indirect methods, has been considered to play an important role in the pathogenesis of hypertension among individuals with obesity from impaired function of the baroreceptor sensitivity [13], increased levels of circulating free fatty acids (FFAs), increased angiotensin II and actions of insulin and leptin. In obesity, primary sodium retention occurs from increased renal tubular reabsorption. Extracellular fluid volume is expanded, resulting in a hypertensive adjustment of the pressure natriuresis providing a model of hypertension because of volume overload [14]. High levels of plasma renin activity (PRA), plasma angiotensinogen, angiotensin II and aldosterone levels have been reported in obesity. Renin–angiotensin system (RAS) has a regulatory mechanism from preventing extreme variations in arterial pressure caused from changes in salt intake and determines obesity-related BP as a salt-sensitive condition. Obesity is accompanied by high levels of circulating insulin and reduced sensitivity to the metabolic actions of insulin. Insulin exhibits a sodium retaining effect through its direct action on the renal tubules, and chronic hyperinsulinemia has been associated with vasoconstriction. Insulin resistance also down-regulate nitric oxide (NO) synthesis, increase vascular and systemic inflammation that can cause endothelial dysfunction. Biologically active derivatives generate from adipose cells, including reactive oxygen species, proinflammatory and inflammatory molecules [interleukin-1β (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-a), C-reactive protein (CRP)] and angiogenetic factors [vascular endothelial growth factor (VEGF)] promote vascular damage, endothelial dysfunction and hypertension.

Treatment of obesity-associated arterial hypertension

Treatment considerations

Patients with obesity and arterial hypertension are exposed to increased metabolic and cardiovascular risk, which should be factored into clinical decision-making. Patients with obesity require more antihypertensive medications to

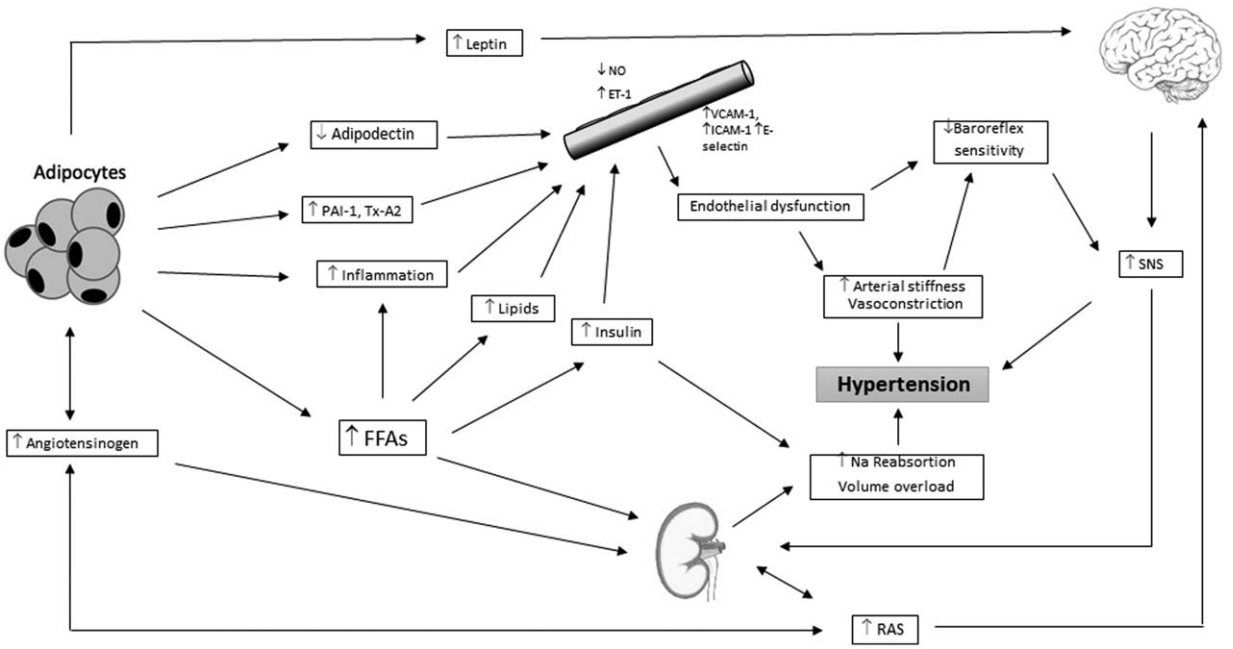

FIGURE 1 Mechanisms of obesity-induced hypertension. Schema developed and modified from Kotsis *et al.* [14].

have their BP controlled and are more likely to be treatment resistant compared with lean patients with arterial hypertension [15]. Yet, current guidelines provide little specific treatment recommendations for this patient population [16]. The state-of-affairs may be explained by a paucity of clinical trials specifically addressing this population. In particular, solid evidence regarding the combination of antihypertensive treatments and weight management is scarce. The following sections will describe the role of weight loss interventions in the management of arterial hypertension and review the evidence for antihypertensive medications. Overall, we propose that patients with obesity require an interdisciplinary and integrative treatment approach. Treatments prescribed for hypertension management should not worsen obesity or diabetes mellitus risk. Conversely, metabolic management should not worsen BP control.

Weight loss in hypertension management

Although excess adiposity is associated with increased BP in susceptible individuals, the role of weight loss in hypertension management is not well supported by clinical trials evidence. Weight reduction can be achieved through lifestyle interventions constituting behavioral modifications, hypocaloric diets and physical exercise [17]. Although these interventions are commonly recommended in patients with obesity and hypertension, average weight loss is modest and most patients regain weight within months to a few years [18]. Much of the data regarding the magnitude of BP reduction with weight loss has been obtained during short-term studies. Furthermore, beneficial effects of weight loss on neurohumoral activity may be greatest during the relatively short active weight loss phase and attenuate with weight stabilization [17].

Over the years, various weight-loss medications have been developed. Some have been withdrawn because of safety concerns (phentermine, sibutramine). Currently, several drugs are approved for body weight management. However, their approval status differs between the United States and Europe. In the United States, phentermine, orlistat, naltrexone/bupropion, phentermine/topiramate, lorcaserin and liraglutide 3 mg are licensed for obesity, but in Europe, only orlistat, naltrexone/bupropion and liraglutide 3 mg are licensed (Table 1). Drugs used for weight management may affect BP indirectly through weight loss, and/or directly through drug-specific actions on cardiovascular mechanisms. For example, on treatment with the serotonin and norepinephrine transporter inhibitor sibutramine (which has been taken off the market), the expected reduction in BP through weight loss was attenuated by drug-specific actions [19]. The mechanism likely contributed to disappointing results in a large scale outcomes trial in which high-risk overweight to obese patients were treated with this drug [20].

TABLE 1. Drugs licensed (not necessarily marketed) in USA and Europe

	USA	EU	Class
Phentermine	√	×	Adrenergic agonist
Orlistat 120 mg tds	√	√	Lipase inhibitor
Orlistat 60 mg tds	√	√	Lipase inhibitor
Sibutramine	×	×	5-HT_{2c}/NE agonist
Naltrexone/Bupropion	√	√	Combination
Phentermine/Topiramate	√	×	Combination
Lorcaserin ER	√	×	5-HT_{2c} agonist
Liraglutide 3 mg	√	√	GLP-1R agonist

Although BP is usually assessed during trials with weight-loss medications, there are no sufficiently large trials having BP as the primary outcome measure. A recent Cochrane meta-analysis assessed influences of weight-loss medications on BP in obese patients with hypertension [21]. Among the currently approved obesity drugs, the authors only included low-dose topiramate/phentermine. Low-dose topiramate/phentermine reduces body weight and BP in obese hypertensive patients [21,22].

For liraglutide, lorcaserin or naltrexone/bupropion, BP responses in people with elevated BP were not available [21]. Yet, mild–modest BP reductions have been observed on treatment with liraglutide [23] and lorcaserin [24]. On naltrexone/bupropion, the expected BP reduction with weight loss was not observed [25]. In fact, BP may slightly, increase likely through monoamine uptake inhibition elicited by bupropion (Fig. 2).

Bariatric surgery massively reduces body weight depending on the type of the procedure but is associated with risks. A recent meta-analysis concluded that bariatric surgery reduces the relative risk for arterial hypertension to 0.54 for up to 5 years [26]. Bariatric surgery may also lead to regression of arterial hypertension in some patients. The risk for arterial hypertension is substantially reduced up to 5 years following bariatric surgery [27], but may depend on the surgical method applied [28]. In the long-term, large sustained body weight loss is required to ameliorate BP [29].

Antihypertensive pharmacotherapy

Eventually, most obese hypertensive patients require antihypertensive pharmacotherapy. The primary goal is to attain BP reduction without worsening obesity and associated metabolic risks (Fig. 2). Current guidelines suggest that in patients with the metabolic syndrome, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and long-acting calcium channel blockers (CCBs) are a preferred choice [16]. None of these drug classes worsens glucose metabolism or weight control. RAS inhibition may have a beneficial effect on glucose metabolism but may not necessarily prevent progression to type 2 diabetes mellitus [30,31]. Compared with RAS inhibitors or CCBs, thiazide-like diuretics may worsen glucose metabolism in a dose-dependent way. Whether or not this metabolic action translates in long-term risks is unclear. In one study of systolic hypertension in the elderly, diuretic-induced hyperglycemia was not associated with worse outcome [32]. One explanation for this could be that the BP-lowering effect in the elderly out-weights the influence of drug-induced hyperglycemia on cardiovascular risk. Treatment with beta blockers (β-blockers) promotes weight gain, limiting their utility in the treatment of patients with obesity [33]. Although all β-blockers tend to increase body weight, weight independent negative influences on insulin sensitivity appear to be attenuated on drugs with vasodilator actions [34]. Obviously, an obese patient with a clear-cut indication for β-blocker therapy, such as heart

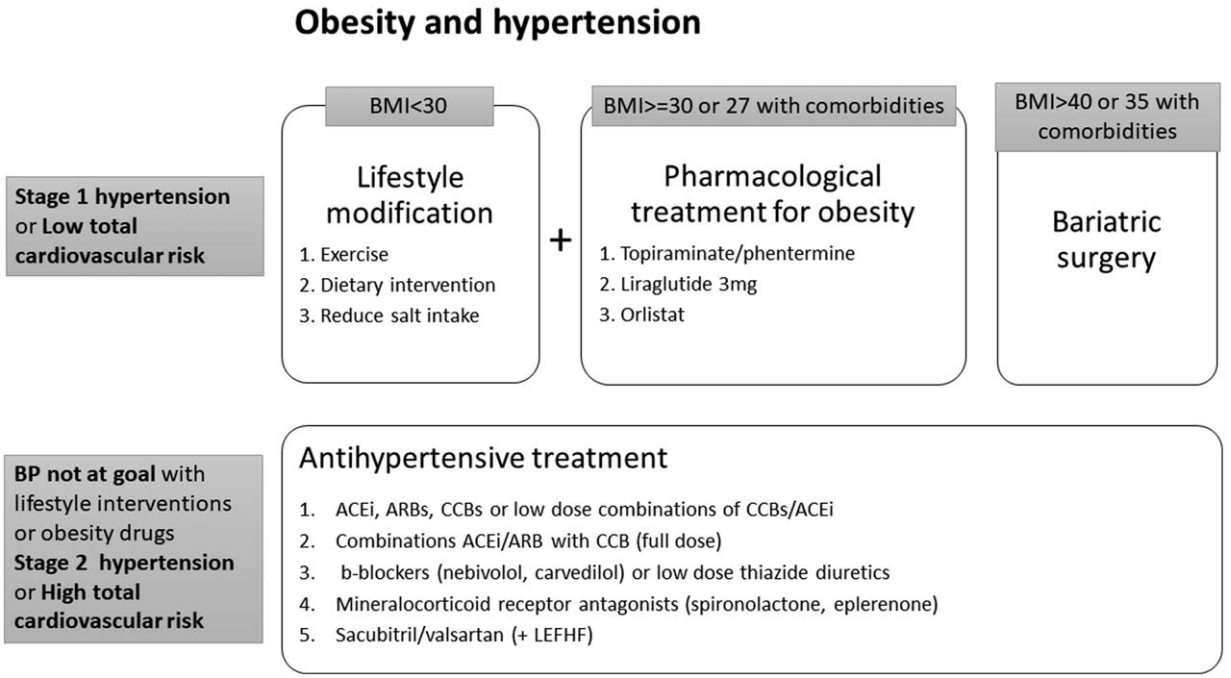

FIGURE 2 Pharmacological treatment of obesity-induced hypertension.

failure with reduced ejection fraction or secondary prevention after coronary heart disease, should receive such treatment.

Obesity is common among patients with treatment-resistant arterial hypertension. It was recently shown that treatment with the mineralocorticoid receptor antagonist spironolactone added to standard therapy is particularly efficacious in controlling resistant hypertension [34]. Mineralocorticoid receptor activation has been implicated in the pathogenesis of obesity-associated metabolic disease [35] supporting the use of mineralocorticoid receptor antagonists in this population. Whereas the renin inhibitor aliskiren has been specifically tested in obese hypertensive patients [36], its role in clinical management is unclear. Combined neprilysin and angiotensin receptor blockade with sacubitril/valsartan lowers BP and improves insulin sensitivity in individuals with obesity and hypertension but is only approved for the treatment of heart failure with reduced ejection fraction. In patients with heart failure, sacubitril/valsartan reduced the progression to type 2 diabetes mellitus [37].

OBESITY AND DIABETES

Epidemiology

Obesity and diabetes mellitus are global health problems and the two epidemics of these diseases are escalating in parallel; their burdens are expected to increase in coming years [38]. Elevated BMI and waist circumference were significantly associated with type 2 diabetes mellitus in men and women [39]. Overweight and obesity account for 44% of the diabetes mellitus cases. World Health Organization (WHO) estimates that, globally, 422 million adults aged over 18 years were living with diabetes mellitus in 2014. The number of people with diabetes mellitus has substantially increased between 1980 and 2014, rising from 108 million to current numbers that are around four times higher [40,41]. The prevalence of obesity-related diabetes mellitus is expected to double to 300 million by 2025 [42]. Data from the International Diabetes Federation indicate that in 2015, more than 415 million persons in the world have diabetes mellitus. It is expected that this number will increase to 642 million by 2040. Amongst countries, China and India have the largest numbers of individuals with diabetes mellitus (109.6 and 69.2 million, respectively) [43]. Regions with the highest prevalence rates of diabetes mellitus are the Pacific Islands and the Middle East, whereas the regions with the lowest prevalence are South and Central America and Africa [44]. The increase in prevalence of diabetes mellitus is linked to economic development and the subsequent changes in lifestyle that promote an obesogenic environment [43]. There is relationship between the degree of excess weight and risk of developing type 2 diabetes mellitus – the risk is increased three-fold with a BMI of 25–29.9 kg/m^2 and 20-fold with a BMI over 30 kg/m^2 [45]. The term diabesity was coined by Sims *et al.* [46] in the 1970s, to highlight the close relationship between diabetes mellitus and obesity [47]. The 'Diabesity' epidemic is likely to be the largest epidemic in human history [48]. Increases in obesity in developed countries began in the 1980s and accelerated from 1992 to 2002, and then in 2006 began to slow; in developing countries, on the contrary, the increase in obesity is likely to continue, and accounts for two-thirds of the current world's obese population [49]. Obesity frequently precedes and is the most important factor in the increase of type 2 diabetes mellitus [50]. The driving physiological force behind the current global type 2 diabetes mellitus epidemic is insulin resistance among overweight and obese persons [51]. The health impact of diabesity includes long-term complications, reduction in health-related functioning,

reduction of quality in life and reduced overall life expectancy [52]. Individuals of certain ethnicities are more prone to develop type 2 diabetes mellitus. Obesity-driven reductions in insulin sensitivity, for example, appears to be behind the dramatic increase in diabetes mellitus prevalence among the Pacific Island populations, as well as among the Pima Indians in the United States, where high levels of obesity and insulin resistance are associated with one of the highest prevalence of type 2 diabetes mellitus in the world [53,54]. However, recently it was postulated that there are two subtypes of type 2 diabetes mellitus: one characterized by marked obesity, insulin resistance and relatively preserved beta cell function (among the Pima Indians) and the other characterized by leaner body mass and more severe beta cell dysfunction (among the Asian Indians) [55]. Depending on the postulated pathogenesis, different therapeutic strategies may be recommended: insulin sensitizers or glucagon-like peptide 1 (GLP-1) analogs for obese people with type 2 diabetes and insulin secretagogues for lean people with type 2 diabetes [43]. In conclusion, current epidemiological evidence indicates that obesity and diabetes mellitus are related multifactorial, complex diseases and a large proportion of the cases are preventable by changing the lifestyles of the patients [38].

Mechanisms and pathophysiology

The close association of obesity with type 2 diabetes mellitus has been termed a syndemic [56,57] and is driven by a common pathophysiology as well as environmental determinants. The hallmark of type 2 diabetes mellitus is the combination of progressive defects in insulin action (insulin resistance) and insulin secretion (ß-cell failure). At the time of diagnosis, ß-cell number and function has declined to 50% of normal [58,59]. Both of these are driven by the excessive deposition of fat within adipose tissue (especially visceral) and ectopically within muscle, liver, pancreas and even the hypothalamus, resulting in systemic and organ-specific low-grade, chronic inflammation [60,61]. Genetic susceptibility also clearly plays a role. Genome-wide association studies have established more than 175 variants for type 2 diabetes mellitus and obesity, but with little shared genetic cause and only accounting for about 15/20% of known heritability [62]. Genetic susceptibility to type 2 diabetes mellitus is mediated both through effects on insulin-release and insulin sensitivity [63]. Epigenetic effects, impairing ß-cell function, are also well described, and can be acquired in utero, or by exposure to lifestyle factors including inactivity and obesity [64].

Adipose tissue is an active endocrine organ that secretes numerous cytokines (adipocytokines) that can have paracrine and systemic effects (Fig. 3), and in obesity exhibits the hallmarks of chronic inflammation. At the same time, obese adipose tissue secretes lower levels of protective anti-inflammatory adipocytokines such as adiponectin.

Weight gain increases fat storage in adipose tissue, but adipogenesis is inhibited by the suppression of peroxisome proliferator-activated receptor gamma (PPARγ) by TNFα [65]. Expansion of existing adipose tissue is thus inevitable, and results in further increased secretion of TNFα, interleukins, plasminogen activator inhibitor-1 and retinol-binding protein-4 amongst others. Secretion of macrophage

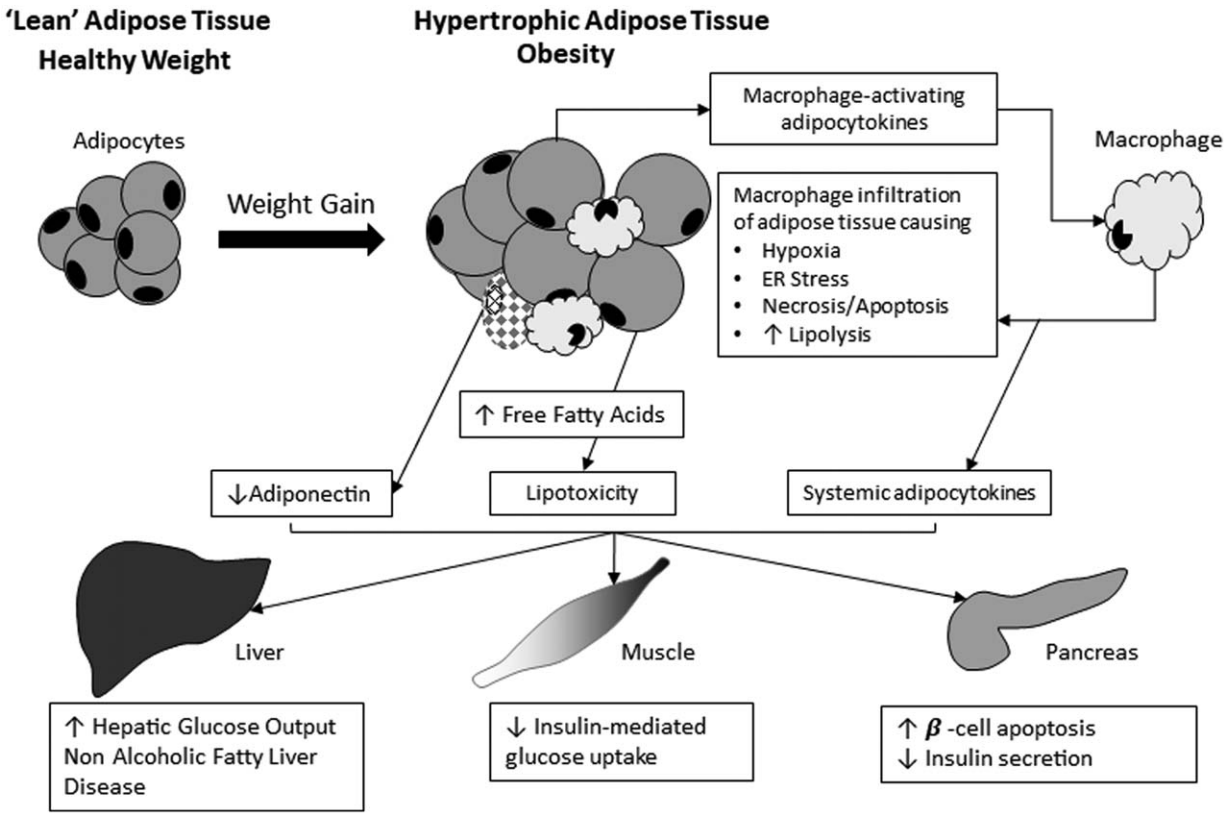

FIGURE 3 Schematic overview linking obesity and type 2 diabetes. Schema developed and modified from Cusi *et al.* [59].

chemoattractant protein-1 (MCP-1) drives macrophage infiltration of adipose tissue (a five-fold increase in obesity is reported [66]) so further increasing cytokine secretion. Hypoxia in the expanded adipose tissue drives further inflammation, endoplasmic reticulum stress, reduced adiponectin secretion and activates inflammatory protein kinase pathways including the c-JUN N-terminal kinase (JNK) and the IκB kinase (IKK) complex [67]. Activation of the IKK complex by inflammation phosphorylates and allows degradation of IkB, an inhibitor of NF-κB, resulting in NF-κB entering the nucleus where it increases expressions of IL-1, IL-6, TNFα, and so forth [61]. In health, insulin has antilipolytic effects by suppressing hormone-sensitive lipase activity within adipose tissue. The result of intra-adipose inflammation and the ensuing insulin resistance is increased output of FFAs into the circulation for ectopic uptake, predominantly by liver and muscle.

The liver is unable to store fat 'safely,' and deposition of fat (hepatic steatosis) and subsequent nonalcoholic fatty liver disease (NAFLD) develop as a result of obesity and insulin resistance [68]. There is a two-way relationship between NAFLD and diabetes mellitus: metabolic syndrome and its components individually predict the development of NAFLD, and vice versa [69]. Between 30 and 75% of people with type 2 diabetes mellitus have NAFLD [70] with a marked increase risk of hospitalization and death from chronic liver disease, cirrhosis and hepatocellular carcinoma [69]. NAFLD increases the risk of developing type 2 diabetes mellitus two-fold [71]. Insulin resistance within the liver is driven by inflammation; activated liver macrophages (Kupfer cells) release cytokines and drive the NF-kB pathway to directly impact on glucose metabolism. Fetuin A and B are recently identified specific hepatocytokines identified in patients with NAFLD and type 2 diabetes mellitus impairing insulin action [68]. Increased FFA secretion from adipose tissue may exceed the liver's capacity to synthesize triglycerides leading to diacylglyceride (DAG) formation and release, which activates protein kinase Cε to impair insulin receptor tyrosine kinase activation [72]. The resulting hepatic insulin resistance results in the failure of hepatic glucose output to suppress both fasting and after meals – the hallmark metabolic disturbance in type 2 diabetes mellitus resulting in hyperglycemia [73–75].

Similar inflammatory processes take place within the pancreas in obesity and drive β-cell apoptosis and dysfunction [76]. Additionally, there is evidence that the incretin actions of GLP-1 are impaired in both obesity and type 2 diabetes mellitus and the resulting hyperglycemia and fasting hyperglucagonemia contribute to the pathophysiology of diabetes mellitus [77]. The interlinking of these processes within the liver and pancreas have been described by Taylor as a twin cycle [74], and support for the pivotal role of fat deposition in the liver and pancreas comes from studies showing reversal of insulin resistance, and restitution of normoglycemia with weight loss be it achieved by diet, pharmacotherapy or weight loss.

Thus, the pathophysiology of obesity and its links to the development of type 2 diabetes mellitus can be seen to be driven by a state of chronic inflammation present within key tissues involved in insulin secretion and action resulting from excess accumulation of fat within and without adipose tissue. The role of gut microbiome in the pathogenesis of type 2 diabetes mellitus is a possible research target in the prevention and treatment of the disease [78].

Treatment

Weight loss strategies: lifestyle intervention

A number of weight-loss strategies are available to treat obesity and the associated insulin resistance including lifestyle-modification programs, pharmaceutical interventions and bariatric surgery. Currently, lifestyle modification is seen as the basis of all obesity treatments and should be lifelong [79]. In a patient-centered approach, behavioral therapy based on self-monitoring of food-intake and physical activity, stimulus control, problem solving and relapse prevention is started. Self-monitoring of food intake and physical activity may be the most important skills as they directly provide the patients with feedback on their behavior allowing them to modify it accordingly [80,81]. Studies have shown that self-monitoring of food-intake and weekly weighing have been predictors of initial weight loss as well as larger weight loss over time [82–84]. Nonetheless, physical activity to increase energy expenditure is still the key component of any weight reduction and weight-loss maintenance program and scientific guidelines recommend at least 150 min/week of moderate aerobic exercise in combination with three weekly sessions of resistance training to increase muscle strength [79,85]. However, physical activity alone has only a moderate effect on weight loss. This effect can be enhanced by the addition of a dietary component such as a low-fat, low-carbohydrate or the Mediterranean-style diet [86–88]. These energy-restricted diets have also beneficial effects on reducing risk factors for cardiovascular disease or type 2 diabetes mellitus [89]. Moreover, the Mediterranean style-diet is known for its beneficial metabolic effects and for its ability to delay need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes mellitus [90]. Additionally, the use of meal replacements or a very low-energy diets can be useful for some patients to support their weight-loss objectives [79,91]. Recently, the power of such diets to reverse type 2 diabetes mellitus has been shown in the DIRECT trial; a total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance allowed almost half of participants to achieve remission to a nondiabetic state and off antidiabetic drugs after one year [92]. However, the diet choice should always be based on the patient's individual food preferences, lifestyle and medical conditions to ensure a sustained diet adherence, which finally determines the success of weight loss and cardiac risk factor reduction [93].

In general, all lifestyle interventions have a modest but significant effect on weight loss in overweight and obese individuals and several studies including the 'Finnish Diabetes Prevention study' and the 'Diabetes Prevention Program' have already proven their effectiveness in the treatment of obesity and prevention of type 2 diabetes mellitus. Both studies demonstrated that weight reduction with intensive lifestyle intervention decreases the incidence of diabetes mellitus by 58% in individuals with impaired

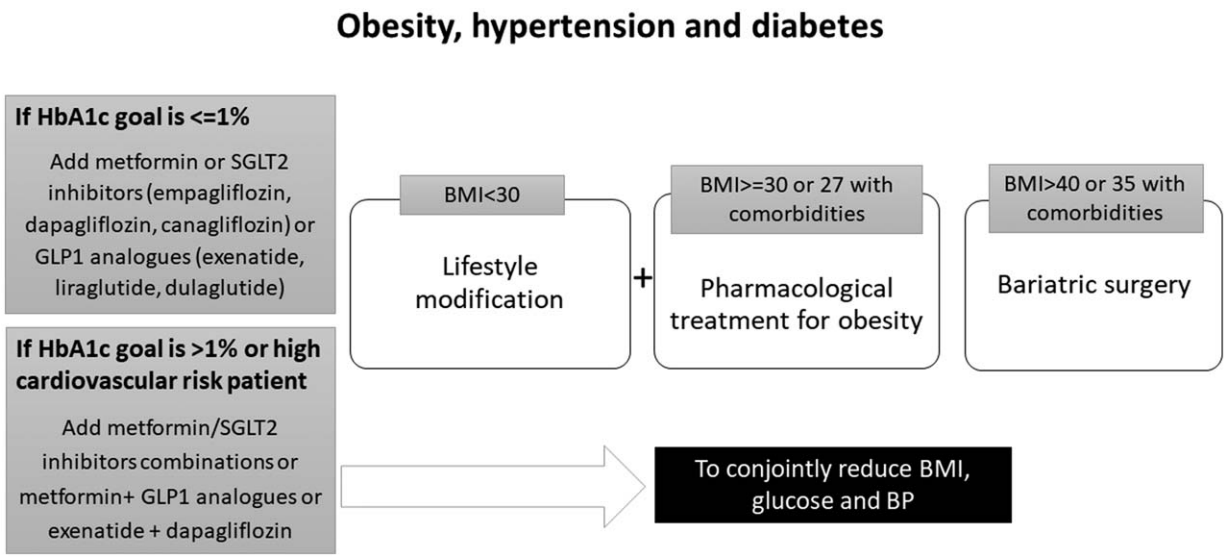

FIGURE 4 Pharmacological treatment of obesity-induced diabetes.

glucose tolerance [94,95]. Lean *et al.* [96] reported that each 1 kg weight loss in the first year of diabetes mellitus diagnosis was associated with 3–4 months of prolonged survival and a weight loss of 10 kg was associated with the restoration of 35% in life expectancy. A modest weight loss of 5–10% seems to be necessary to reduce hemoglobin A1c (HbA1c) levels and decrease the use of hyperglycemic, hypertension and lipid-lowering medications as observed after 1 year in the Look AHEAD study [97–99]. This amount of weight loss also supports the reduction of depression symptoms and the remission of obstructive sleep apnea (OSA) or at least reduced severity [100,101]. However, achieving this level of weight loss requires intensive lifestyle interventions including regular physical activity and an energy-restricted diet. Thus, lifestyle changes are quite often difficult to achieve and to maintain for a longer period of time. Most patients who have lost substantial weight through lifestyle change typically regain about 30–35% of their lost weight in the year following treatment and more than 50% of these patients most likely return to their baseline weight after 5 years [102]. Consequently, weight loss using lifestyle interventions is quite often seen as of temporary benefit, and alternative options such as appropriate antiobesity medications should be considered for those patients, who are still struggling with their weight management objectives.

Pharmaceutical interventions

Although lifestyle counseling is the first-line therapy in the treatment of obesity and type 2 diabetes mellitus, pharmacologic agents can be added as part of a comprehensive weight-loss strategy.

Antiobesity drugs as primary therapeutic option

Antiobesity agents may help patients to lose and maintain weight, improve their quality of life and may be beneficial in the prevention of obesity-related comorbidities. Currently, these drug therapies are recommended for patients with a BMI at least 30 kg/m^2 or a BMI at least 27 kg/m^2 with an obesity-related comorbidity (e.g. hypertension, type 2 diabetes mellitus, OSA; Fig. 4) [103]. Antiobesity agents have shown to support patients with type 2 diabetes mellitus by reaching their weight-loss goals and improving their Hb1Ac-levels [104,105]. Thus, the ability to target overweight/obesity and thereby improving poor glycemic control simultaneously represents a novel approach in the management of type 2 diabetes mellitus. However, evidence-based recommendations on using antiobesity drugs in the diabetes mellitus management are not part of present guidelines as relatively few studies with weight loss as primary target in diabetes mellitus patients have been performed so far. Further studies, and integration of evidence from them into diabetes mellitus management guidelines are urgently needed.

Effects of concomitant medication

The primary focus of weight management is the prevention of additional weight gain. Awareness of the potential weight effects when selecting pharmacologic agents for the treatment of obesity complications is important. Unfortunately, many of these treatments can lead to unwanted weight gain, which could finally offset the benefits. Patients with diabesity face the problem that most of the traditional antidiabetic drugs promote weight gain [106], which renders the management of most overweight or obese individuals with type 2 diabetes mellitus even more challenging. Thus, glucose-lowering agents, which are weight neutral [metformin, dipeptidyl peptidase-IV (DPP-IV-inhibitors)] or support weight loss, should be the first choice for their treatment [sodium-glucose co-transporter 2 (SGLT2)-inhibitors and GLP1-analogues; Figure 4] [107]. In patients with type 2 diabetes mellitus and hypertension, empagliflozin, canagliflozin and dapagliflozin reduced SBP and DBP and body weight versus placebo, irrespective of the use of other antihypertensive drugs [108–110]. In a randomized, controlled trial that compared liraglutide, a GLP1 receptor analogue, with placebo in patients with type 2 diabetes mellitus and high cardiovascular risk liraglutide resulted in

lower body weight and SBP but higher DBP and heart rate [111]. Results from a pooled analysis of liraglutide 3 mg daily clinical trials suggest no increased risk and a possible benefit of liraglutide 3 mg on cardiovascular safety in an overweight and obese population [112]. Dulaglutide 1.5 mg was also associated with a reduction in body weight and 24 h SBP and an increase in 24 h heart rate [113]. The latter is probably a class effect of GLP1 receptor analogues related to GLP1 receptors on the sinoatrial node [114]. Combining exenatide with dapagliflozin was significantly superior to either drug alone for weight loss and greater reductions in SBP [115].

Additionally, the use of some antipsychotics, antidepressants, antiepileptics and steroid hormones, which are associated with weight gain, should be minimized and alternatives should be provided, whenever weight loss is an objective [107].

Weight-loss strategies: bariatric (metabolic) surgery

Bariatric surgery is currently the most effective long-term weight-loss strategy for overt obesity. It is recommended for individuals aged 18–60 years with a BMI at least 40 kg/m^2, or for patients with a BMI at least 35 kg/m^2 and obesity-related comorbidities, such as type 2 diabetes mellitus. Bariatric surgery results in approximately 15–40% weight loss of initial body weight [116], which is associated with significant improvements of comorbidities (e.g. type 2 diabetes mellitus) and reduces the overall mortality [117–119]. Additionally, bariatric surgery also influences psychological and health-related quality of life. Nonetheless, bariatric surgery candidates should be carefully selected as long-term nutritional or micronutrient deficiencies, malnutrition or osteoporosis may occur [120]. Following that, multidisciplinary lifelong postoperative follow-up is recommended and required. To facilitate this lifelong surveillance of bariatric surgery patients, the Obesity Management Task Force of the European Association recently published a comprehensive review, wherein major clinical points in bariatric medicine are discussed and some practical recommendations for the postsurgery medical management are stated [121]. Although bariatric surgery is highly effective in achieving it is expected that 20–25% of the weight lost will be regained over a period of 10 years after the intervention [116]. Bariatric surgery is superior to other interventions in achieving long-term sustained weight loss in morbidly obese patients, but randomized controlled trials targeting the prevention of weight regain after surgical procedures are needed to identify causative factors and interventional strategies. Bariatric surgery gained increasing interest as a potential treatment approach for type 2 diabetes mellitus as it is associated with substantial improvements in diabetes mellitus and/or complete diabetes mellitus remission [116,122]. Due to the observed beneficial metabolic effects [123], bariatric surgery is also referred to 'metabolic surgery' and is nowadays recommended as treatment option for type 2 diabetes mellitus [124,125]. In general, the obtained diabetes mellitus remission rates vary between 45 and 95% depending on the type of procedure – resulting in higher remission rates following surgical procedures, which induce greater weight loss [126–128]. Moreover, several studies demonstrated that bariatric surgery is superior to intensive medical interventions regarding weight reduction and metabolic processes including the STAMPEDE trial. In the current 5-year follow-up report, the authors demonstrated that the beneficial effects of bariatric surgery on blood glucose levels in mild and moderately obese individuals with type 2 diabetes mellitus may persist up to 5 years, with the advantage over diabetes mellitus medications [129]. Currently, the physiological and molecular mechanisms underlying these beneficial effects are incompletely understood. It is suggested that a constellation of gut-derived neuroendocrine changes rather than a single mechanism might be responsible for the observed postoperative glycemic improvements. However, type 2 diabetes mellitus recurrence or worsening in patients with initial resolution or improvement can be observed after years as shown by the follow-up report of the SOS trial [116]. Noteworthy, 50% of the patients, who underwent surgery with remission of diabetes mellitus at 2 years, relapsed after 10 years. Interestingly, a greater likelihood of diabetes mellitus relapse was associated with less initial weight loss and greater weight regain [130,131]. Following that, further long-term studies assessing the durability of diabetes mellitus remission are warranted – in particular, whenever bariatric surgery shall be considered for younger adults or adolescents.

OBESITY AND DYSLIPIDEMIA

Lipids in patients with obesity

The NHANES study shown that dyslipidemia is the most common comorbidity associated with obesity followed by hypertension and diabetes mellitus [132]. In obesity, atherogenic dyslipidemia is prevalent contributing significantly to cardiovascular risk [133]. Lipolysis of triglyceride-rich lipoproteins is impaired by reduced mRNA levels of lipoprotein lipase (LPL) in adipose tissue and reductions in LPL in skeletal muscle as well as competition for lipolysis between very low-density lipoprotein (VLDL) and chylomicrons. Increased postprandial lipemia results in elevated levels of FFAs and triglycerides. In the presence of hypertriglyceridemia, the triglyceride content of LDL increases. The triglyceride within LDL are hydrolyzed by hepatic lipase leading to the formation of small dense LDL, which are more atherogenic. Furthermore, remnants are also atherogenic because they can penetrate the arterial wall. High-density lipoprotein (HDL) is also affected because the increased number of triglyceride-rich lipoprotein increases cholesteryl ester transfer protein (CETP) activity. Cholesterol ester of HDL is exchanged to triglyceride. triglyceride-rich HDL becomes a substrate for hepatic lipase resulting in small HDL particles with reduced affinity to apoA1 impairing reverse cholesterol transport [134]. A particle should be small enough to penetrate the arterial wall to initiate the atherogenic process. Although chylomicrons and large VLDL are unable to pass through the arterial intima, small VLDL and LDL are able to penetrate the intima and have been shown to be associated with the presence of severity and progression of atherosclerosis. In obesity, the parameter that best correlates with increased BMI is hypertriglyceridemia. As BMI and waist circumference increase, it has been shown that triglyceride and apoprotein-B levels go up [135].

Which lipid parameter captures the risk caused by these changes in obese patients? Remnants and triglyceride-rich lipoproteins are increased in obesity. Normally, LDL cholesterol and non-HDL cholesterol (=Total cholesterol − HDL cholesterol) are concordant. However, in insulin-resistant states, such as obesity, LDL and non-HDL may be discordant and non-HDL and apo-B may be superior to LDL in risk prediction in obese patients [136]. Non-HDL cholesterol includes the cholesterol in VLDL and is a better surrogate for LDL particle number. Therefore, non-HDL cholesterol may have an additional diagnostic value in obese patients.

In summary, the following *four points* concerning lipids in obese patients are important. *Dyslipidemia* in obesity represents a cluster of lipid and lipoprotein abnormalities including elevation of both fasting and postprandial triglyceride, apoB, and small dense LDL as well as low HDL and apoA1. *Non-HDL-C* or apoB are good surrogate markers of triglycerides and remnants and are a secondary objective of therapy. Non-HDL-C less than 3.4 mmol/l (<130 mg/dl) or apoB less than 100 mg/dl is desirable in those at high-risk, less than 2.6 mmol/l (<100 mg/dL) or apoB < 80 mg/dl, respectively, in those at very high risk. *Increased* waist circumference and elevation of triglyceride seems to be a simple tool to capture the high-risk patients with metabolic syndrome. *Atherogenic dyslipidemia* is one of the major risk factors for cardiovascular disease in people with type 2 diabetes mellitus [137].

Mechanisms and pathophysiology

Increased adipose tissue mass increase FFAs into the circulation. FFA release from adipose tissue is suppressed by insulin in both lean and obese individuals but in obesity, the process is insulin resistant. FFA release per unit fat mass is less in obese individuals than in lean individuals. However, because of the increased fat mass, total FFA delivery to the circulation is increased in obesity. Despite high-plasma insulin concentrations in response to a standard meal, obese individuals fail to suppress FFA release from adipose tissue. Increased availability of fatty acids will decrease glucose utilization in muscle and stimulate hepatic glucose production. Adipose tissue is an important site for the disposal of dietary triacylglycerol in the postprandial period. Obesity is typically characterized by increased postprandial lipemia, reflecting at least in part prolonged circulation of dietary fatty acids. These fatty acids will be removed by several tissues, including skeletal muscle, pancreas and liver instead of adipose tissue. In obesity, adipose tissue overloaded with triacylglycerol has reduced buffering capacity for lipid storage in adipocytes. Fat cells fail in their normal role to protect other tissues from the daily influx of dietary fatty acids [138,139]. Lipolysis of triglyceride-rich lipoproteins is impaired in obesity by reduced mRNA expression levels of LPL in adipose tissue [140], reductions in LPL activity in skeletal muscle and competition for lipolysis between VLDL and chylomicrons. The increased synthesis of VLDL in the liver can inhibit lipolysis of chylomicrons, which promotes hypertriglyceridemia. The free VLDL particles undergo enzymatic exchanges with other lipoprotein particles such as HDL and LDL, via CETP. Once these triglyceride-rich lipoprotein particles are exposed to various lipases, then the HDL particles become smaller and undergo metabolism and excretion by the kidney, resulting in decreased HDL levels. In the presence of hypertriglyceridemia, the cholesterol-ester content of LDL decreases, whereas the triglyceride content of LDL increases by the activity of CETP. The increased triglyceride content within the LDL is hydrolyzed by hepatic lipase, which leads to the formation of small, dense LDL particles. Small dense LDL are relatively slowly metabolized with a 5-day circulating time, which promotes its atherogenicity. The VLDL particles also undergo lipolysis, resulting in VLDL remnants and consequently formation of small, dense LDL particles.

In conclusion, obesity-induced dyslipidemia is characterized as overproduction of VLDL by the liver, decreased triglyceride lipolysis, increased FFA fluxes from adipocytes to the liver and the formation of small-dense LDL particles.

Treatment

Targets of treatment

Despite patients with obesity commonly exhibiting mixed atherogenic dyslipidemia with elevated triglycerides and low HDL cholesterol levels, the primary target of hypolipidemic treatment is the reduction of LDL levels. According to the ESC/EAS guidelines for the management of dyslipidemias, LDL cholesterol should be reduced to less than 1.8 mmol/l (70 mg/dl) and 2.5 mmol/l (100 mg/dl) in very high-risk and high-risk patients, respectively [141].

Lifestyle recommendations

Lifestyle modification to reduce body weight by 5–10% should be the first step as this is shown to improve lipid profiles [142]. Consumption of fruits, vegetables, legumes, nuts, wholegrain cereal foods and fish is recommended, whereas foods rich in trans-fat and saturated fat, as well as the intake of beverages and foods with added sugars, should be avoided. Regular physical activity (for at least 30 min every day) can favorably alter lipid and lipoproteins independently of significant body weight change [143]. Alcohol restriction may generally contribute to the decrease of body weight and is essential for the treatment of hypertriglyceridemia in some patients [144].

Drug treatment

With the exception of orlistat, which decreases LDL levels to a greater degree than expected with diet alone, phentermine/topiramate, lorcaserin, naltrexone/bupropion and liraglutide affect serum lipid levels mainly by inducing a greater weight loss compared with diet alone [144]. Thus, many obese individuals with borderline increased serum lipid levels may normalize their serum lipid profile with the antiobesity drug-assisted weight loss accompanied with lifestyle changes.

Statins, that mainly reduce LDL cholesterol levels, are the cornerstone of hypolipidemic treatment in the general population as well as in obese patients. Even though, statin-outcome trials have not examined the beneficial effects of hypolipidemic therapy especially in patients with obesity, subgroup analyses have shown that there is no difference in the reduction of cardiovascular events

between patients with BMI greater than 30 kg/m^2 and less than 25 kg/m^2 [145,146]. However, statins exhibit a dose-dependent detrimental effect on glucose homeostasis, especially in patients with underlying abnormalities of glucose homeostasis, which is the case in a considerable proportion of obese patients [147–149]. Even though the underlying mechanisms of the statin-associated diabetes mellitus are not clear [146,150], one study showed that statin treatment is associated with body gain that is in part responsible for the drug-induced new-onset diabetes mellitus [151]. Thus, careful lifestyle recommendations should be given to patients with obesity and prediabetes before starting statin therapy [152]. It should be noted that especially in high-risk and very high-risk obese patients with significantly increased LDL cholesterol levels, the initiation of statin treatment should not be delayed because of the above side-effects or awaiting the results of lifestyle changes.

If the LDL cholesterol goals are not achieved with the maximally well tolerated statin therapy, then combination of statins with ezetimibe is recommended [153]. Even though ezetimibe is well tolerated, the drug's long-term effects on carbohydrate homeostasis are not well known [154,155]. Bile acid sequestrates can also be used for a further decrease of LDL cholesterol in combination with statins and these drugs may also improve carbohydrate metabolism. However, these drugs can increase triglyceride levels and should be carefully used in obese patients with hypertriglyceridemia [144,153]. Finally, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab/alirocumab) can also be used on top of maximally well tolerated doses of hypolipidemic treatment in very high-risk obese patients, in obese patients with heterozygous familial hypercholesterolemia or in those with statin intolerance who have not achieved their recommended LDL cholesterol targets [156].

In patients with increased triglyceride levels, all possible secondary causes of hypertriglyceridemia (including a high-carbohydrate diet, alcohol and drugs affecting triglyceride-rich lipoproteins metabolism) should be checked and appropriately managed [153]. In patients with obesity despite appropriate lifestyle intervention, statin therapy such as rosuvastatin, atorvastatin or pitavastatin can significantly reduce serum triglycerides [153]. In high-risk obese patients with serum triglycerides greater than 2.5 mmol/l (especially in those with simultaneously low-HDL cholesterol levels) despite appropriate well tolerated statin therapy, fenofibrate can be used in combination with statins [157]. Fenofibrate on top of a statin is safe and well tolerated, however its dose should be carefully adjusted in individuals with chronic kidney disease (CKD), while the drug can induce a modest reversible increase in serum creatinine levels [144]. In obese patients with severe hypertriglyceridemia who exhibit elevated triglyceride levels despite appropriate statin therapy (±fenofibrate), ω-3 fatty acids (2–4 g/d) can be used to further dose-dependently decrease triglyceride levels. This treatment is well tolerated though the effects of ω-3 fatty acids on cardiovascular morbidity and mortality are not well established [144,153,158].

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Conflicts of interest

V.K. has participated in advisory board meetings or honoraria for Vianex, Elpen, Boehringer-Ingelheim, Lilly, Merck, Servier, Amgen, Sanofi, Menarini, Ciezi, Astra-Zeneca and Novartis, N.F. is an employee of Novo Nordisk, views expressed are personal, P.N. has participated on advisory board meetings for Novo Nordisk related to diabetes and CVD, L.T. has participated in advisory board meetings or honoraria for Merck, Abbott, Amgen, Sanofi, Daichi Sankyo, Astra, Actelion, Novartis, Pfizer, Bayer, Servier, Recordati, Mylan, Novo Nordisc and Sanovel. All other authors indicate no conflicts of interest.

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