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OBESITY AND DYSLIPIDEMIA – REDUCTION TARGETS; USE OF DIETS AND DRUG PRODUCTS

OBESIDADE E DISLIPIDEMIA – METAS DE REDUÇÃO; USO DE DIETAS E MEDICAMENTOS

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ABSTRACT

Cardiovascular disease has been the no. 1 cause of death in Brazil since the late 1960s, despite the downtrend observed in recent years. Lifestyle changes related to urbanization and globalization, high calorie intake and lower energy expenditure, combined with a rapidly aging population due to increased life expectancy, have led to a greater prevalence of obesity and dyslipidemia, and consequently, cardiovascular and metabolic diseases. Population-based surveys, cohort and case-control studies underline the importance of the growth of risk factors, and regional differences indicate that public policies and medical care must prioritize health interventions in order to prevent and control the most prevalent risk factors in our country. The therapeutic approach to obesity must include not only weight reduction alone, but also in combination with comprehensive metabolic improvement, which is associated with a reduced risk of cardiovascular complications. In general, weight loss is more frequently achieved in the first few months or first year of exposure to medications, and although some drugs are more effective, adverse events are common, limiting treatment options to long-term therapy. The major advances and greater safety seen in recent years were achieved with the use of anti-hyperglycemic agents such as GLP-1 analogues, enabling long-term use with maintenance of results and adding cardiovascular benefits. The therapeutic approach to dyslipidemia in obese patients is imperative for the progress of this patient population, in which multiple physiological, biochemical, metabolic and clinical factors are interlinked and directly related to substantial increases in the risk of diabetes, atherosclerotic cardiovascular disease, and all-cause mortality.

Keywords: Obesity; Dyslipidemia; Epidemiology; Treatment; Lifestyle.

RESUMO

As doenças cardiovasculares continuam sendo a principal causa de morte no Brasil desde o final da década de 1960, a despeito da tendência de queda observada nos últimos anos. A mudança de estilo de vida relacionada à urbanização e globalização, com alta ingestão calórica e menor gasto energético, o rápido aumento da população idosa devido à maior expectativa de vida levaram à maior prevalência de obesidade e dislipidemias e, consequentemente, doenças cardiovasculares e metabólicas. Pesquisas de base populacional, estudos de coorte e de caso e de controle apontam para a importância do crescimento dos fatores de risco e diferenças regionais indicam que as políticas públicas e o atendimento médico devem priorizar intervenções de saúde tendo como objetivo a prevenção e controle dos fatores de risco mais prevalentes em nosso meio. A abordagem terapêutica da obesidade deve incluir não apenas a redução isolada do peso, e sim, atrelada à melhora metabólica ampla que se associe à diminuição do risco de complicações cardiovasculares. De um modo geral, a perda de peso é mais frequentemente alcançada ao longo dos primeiros meses ou do primeiro ano de exposição aos fármacos e embora alguns sejam mais efetivos, eventos adversos são frequentes, limitando o tratamento a longo prazo. O grande avanço e a maior segurança nos últimos anos vieram com o uso de medicamentos anti-hiperglicemiantes, como análogos de GLP-1, permitindo o uso a longo prazo com manutenção de resultados e adicionando benefícios cardiovasculares. A abordagem terapêutica das dislipidemias no paciente obeso é imperativa para a evolução desse perfil de pacientes, nos quais múltiplos fatores fisiológicos, bioquímicos, metabólicos e clínicos, estão interconectados e diretamente relacionados com aumentos substanciais do risco de diabetes, de doença aterosclerótica cardiovascular e mortalidade por todas as causas.

Descritores: *Obesidade; Dislipidemias; Epidemiologia; Tratamento; Estilo de Vida.*

EPIDEMIOLOGY OF OBESITY AND DYSLIPIDEMIA

Epidemiological transition in Brazil

The most important epidemiological transition occurred in Brazil in the 1960s, when chronic non-communicable diseases (NCDs) became the leading cause of mortality surpassing infectious diseases and nutritional deficiencies. This transition occurred along with increasing urbanization, better health and nutritional care, increasing immunization coverage, and the country's economic growth.[1,2] However, this has resulted in a triple burden of disease due to continued mortality from infectious diseases, the increase in external causes of death (homicides, traffic accidents), and the increase in mortality from non-communicable diseases. Since the late 1960s, cardiovascular diseases have been the main cause of death in Brazil. Two important trends have contributed to the maintenance of these statistics in recent decades:[1,3] The first was the change in lifestyle due to urbanization and globalization, such as higher calorie intake and lower energy expenditure.[1,4] The second was the rapid aging of the population due to higher life expectancy and lower fertility.

Health behavior trends show that, between 1989 and 2013, smoking declined from 43.3% to 19.2% and 27% to 11.2% for men and women, respectively. However, from 1975 to 2013 there was a marked increase in the prevalence of overweight and obesity, making obesity one of the most challenging public health problems in Brazil. (Figure 1) The increase in obesity was more pronounced in men, in rural areas, and among individuals with lower incomes.[5] The physical activity data were obtained more recently from the Surveillance System of Risk Factors and Protection for Chronic Diseases by Telephone Survey (VIGITEL), with a representative sample of adults in 27 capitals and the Federal District. From 2006 to 2012 VIGITEL data showed an increase in physical activity and leisure time in adults, particularly young adults.[6] However, in 2013, a high proportion of adults (39.8% of men and 51.5% of women) still did not reach the recommended levels of physical activity (light or moderate physical activity for at least 150 minutes per week, or intense physical activity for 75 minutes per week), including leisure, work and transportation activities.[7]

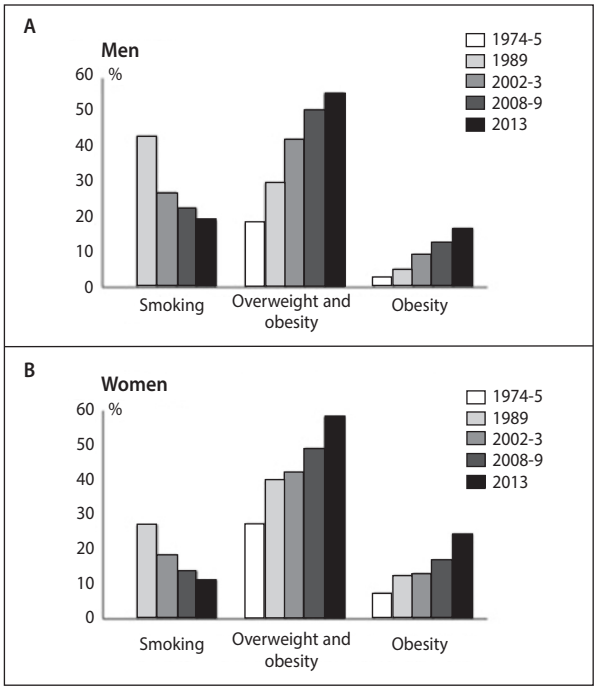

Figure 1. Prevalence of smoking, overweight and obesity (including BMI ≥25 kg/m2), and obesity (BMI ≥30 kg/m2) in adults, obtained from population-based surveys in Brazil from 1975 to 2013. No smoking data for 1974-1975.7 A, men; B, women. Data from the Brazilian Institute of Geography and Statistics (IBGE; www.ibge.gov.br) and National Health Survey, 2013. BMI = body mass index.

In relation to dyslipidemia, the largest survey was conducted in 2002 by the Brazilian Society of Cardiology. This study examined a convenience sample of 81,262 volunteers ≥ 18 years old (mean 44.7 years) recruited from 13 Brazilian cities.[8] The mean cholesterol value (SD) was 199 (35) mg/dL; 40% of the study population had cholesterol > 200 mg/dL and 14% of this population had cholesterol > 240 mg/dL. Cholesterol increased with increasing age and was similar between men and women. However, in addition to working with a convenience sample, this research did not collect information on the use of hypolipidemic agents.[8] Other regional population-based studies reported the prevalence of total cholesterol ≥ 240 mg/dL ranging from 4.2% to 31.3%, and unlike diabetes mellitus, hypertension and smoking, dyslipidemia was more frequent in those in higher socioeconomic groups. Data from six population-based surveys examining the prevalence of metabolic syndrome in urban and rural areas showed that 53.9% of men and 67.5% of women have HDL-c < 40 and < 50 mg/dL, respectively.[9] The prevalence of elevated triglycerides varied from 13-17% in these studies. Data from the ELSA-Brazil cohort[10] show that despite the use of statins, the prevalence of hypercholesterolemia (>200 mg/dL for total cholesterol) and hypertriglyceridemia (≥150 mg/dL) was 61.5% and 31.2%, respectively. Although the prevalence of hypercholesterolemia was similar among men and women (58.9% and 63.6%, respectively), hypertriglyceridemia was almost twice as frequent in men (40.9% vs. 23.0%).[10]

Along with the obesity epidemic and the rapid aging of the population, the prevalence of diabetes mellitus is also growing in Brazil. The only population-based multicenter study to evaluate diabetes mellitus using blood samples was conducted in nine large Brazilian cities between 1986 and 1988 with a randomized sample of 21,847 individuals aged 30 to 69 years and reported a prevalence of diabetes of 7.6%, with no differences between men and women.[11] Based on data obtained from the VIGITEL study, with younger individuals, 18 years of age and older, there was a 24% increase in the prevalence of self-reported diabetes in Brazilians from 2006 to 2013 (5.5% to 6.8%).[12] On the other hand, in the baseline evaluation of ELSA-Brazil data (2008-2010), 20% of adults between the ages of 35 to 74 years had diabetes mellitus, defined by the presence of previously diagnosed (self-reported or by the use of medication) or undiagnosed diabetes mellitus (based on fasting glucose values, oral glucose tolerance tests, or altered glycated hemoglobin).[13]

Although there are many studies on the prevalence of cardiovascular risk factors, several have limitations because they are not representative of the country or because of the absence of laboratory confirmation. VIGITEL is one of the best sources of information. Although it is a study conducted

by telephone, it was only conducted in the state capitals and includes only self-reported data from large urban cities, which may lead to underreporting bias.

The INTERHEART study, a Latin American branch, indicated that abdominal obesity, dyslipidemia, smoking, history of hypertension and diabetes, and lack of regular physical exercise contributed to more than 86% of the attributable population risk for myocardial infarction in the region.[14] The Brazilian branch of INTERHEART included 313 cases and 364 age- and gender-matched controls. The highest risk attributable to the population was observed for the ApoB/ApoA-1 ratio (57.0%; 95% CI, 38.6%-73.4%), waist-to-hip ratio (51.0%; 95% CI, 27.2%-74.4%), permanent stress (43.8%, 95% CI, 25%-64.7%), hypertension (43.2%; 95% CI, 35.4%-51.4%), and smoking (40.3%, 95% CI, 28.9%-52.8%).[14] In the AFIRMAR (*Acute Myocardial Infarction Risk Factor Assessment in Brazil*) study, a case-control study, the independent risk factors for myocardial infarction showed a conventional pattern (smoking, diabetes *mellitus*, and central obesity, among others) with different association forces.[15] Most of the risk factors described are avoidable and preventable through the implementation of appropriate policies. The INTERSTROKE study,[16] which used a similar methodology, demonstrated that in a community in the South Region of Brazil, the combination of arterial hypertension, atrial fibrillation, left ventricular hypertrophy, presence of carotid plaque, heavy smoking, diabetes mellitus, alcohol abuse, low HDL-c levels, and physical inactivity explained 98.9% of the incidences of ischemic stroke. According to the PURE (*Prospective Urban and Rural Epidemiological*) study, protective behaviors in the development of cardiovascular diseases (healthy diet, regular physical activity, no smoking) are adopted less frequently by populations living in low- and middle-income countries.[17] This same pattern occurs in Brazil, where studies have shown a higher prevalence of cardiovascular risk factors, especially smoking, hypertension and obesity in lower socioeconomic groups. [1,13,18]

Life expectancy in Brazil was generally observed to increase at birth from 1990 to 2015, but with important heterogeneity among the states. The reduction in mortality from infectious diseases was the largest contributor to higher life expectancy in most states of the North and Northeast. On the other hand, the reduction in mortality from cardiovascular diseases was the largest contributor to higher life expectancy in the South, Southeast, and Central-West Regions. However, in men, external causes have reduced life expectancies in 17 of the 27 states. Although death rates related to age-adjusted ischemic heart disease (IHD) and cerebrovascular disease (CVD) have declined over time, they remain the leading causes of death in the country. On the other hand, the causes of premature death have changed substantially. Death due to diarrheal conditions has moved from 1st to 13th place, and then to 36th place, respectively, while violence has changed from 7th to 1st and then to 2nd place.[19]

Thus, public policies and medical care should prioritize health interventions aiming at the prevention and control of the most prevalent risk factors in our environment.

TREATMENT OF OBESITY

An increase in adipose tissue is associated with a chronic inflammatory state due to the infiltration of macrophages and lymphocytes modifying the synthesis and release of cytokines that are associated with reduced insulin sensitivity.[20-23] Thus, obesity is closely linked to carbohydrate and lipid disorders. Consequently, the treatment of obesity should include not only isolated weight reduction but also a broad metabolic improvement associated with reduced risk of cardiovascular complications.[24-29] In addition, in the presence of obesity and increased blood glucose the formation of glycated end products, reduction of adiponectin, increase in proinflammatory cytokines, and greater expression of prothrombotic factors are associated with endothelial dysfunction, atherosclerosis, and thrombotic events.[26, 30-33]

Thus, considering that most obesity interventions are only partially successful in obtaining an ideal weight, it is important that the drugs used in the treatment of obesity have additional antihyperglycemic, anti-inflammatory, antithrombotic, and hypolipidemic effects, provide improvement in endothelial function, and mitigate cardiovascular disease mechanisms. Another interesting aspect linking obesity and diabetes to cardiovascular disease is their frequent association with vascular calcification.[34]

A deficiency in the vitamins D and K2 seems to be associated with greater vascular calcification, activation of the angiotensin renin system and the sympathetic nervous system.[35-39]

Obesity and the concomitance of diabetes is associated with disorders of incretin levels, which contribute to greater post-prandial hyperlipidemia, and disorders of satiety and glucose metabolism, which are associated with impairment of the diversity of relevant actions mediated by incretins in the cardiovascular system.[40-43]

Drug treatment

Even with the availability of some safer and more effective medications in recent years, the concomitant non-pharmacological treatment is essential and includes a healthy and adequate diet combined with an individualized physical activity plan.

In general, weight loss is most frequently achieved during the first months or first year of exposure to drugs, and although some are more effective, adverse events are frequent, limiting long-term treatment. The great advance and greater safety in recent years came with the use of antihyperglycemic drugs as GLP-1 analogues, allowing long-term use with maintenance of results and adding cardiovascular benefits.

Orlistat

This gastric and pancreatic lipase inhibitor is a drug approved in our country for the treatment of obesity and must be prescribed at a dose of 120 mg three times a day with meals. Orlistat inhibits approximately 30% of fat absorption from the diet, causing an increase in fecal fat elimination.[44]

Favorable results were observed with orlistat in a study developed in Sweden, showing improvement in the lipid and glycemic profile in addition to weight loss. [45] More recently, a meta-analysis involving 33 randomized studies showed a mean weight loss of 2.12 kg and confirmed metabolic benefits, particularly in the lipid and safety profiles.[46]

Liraglutide

This glucagon like peptide-1 (GLP-1) analog was also approved in Brazil for weight reduction in patients with body mass index ≥ 27 kg/m2 and at least one additional risk factor.[47,48]

The drug should be administered subcutaneously in gradual doses until the goal of 3.0 mg is reached, with dose-dependent weight loss. The drug produces satiety and provides several cardiovascular benefits, including mild but significant improvement in the lipid profile.

In a placebo-controlled, double-blind study over 56 weeks involving 3731 non-diabetic patients who were obese or overweight, exposure to the drug was associated with a mean loss of 8.4±7.3 kg of weight and in the placebo arm the loss was 2.8±6.5 kg (difference of 5.6 kg) [29].[48] The study showed that exposure to the drug resulted in a loss of at least 5% in approximately 2/3 of patients and more than 10% in 1/3 of patients. In addition, it confirmed several cardiovascular and metabolic benefits, such as reduction of inflammatory and thrombotic biomarkers and insulin sensitivity. Benefits in the lipid profile were also observed and the treatment was safe, with only some gastrointestinal disorders being observed, mainly nausea at the beginning of the treatment.[48] The drug was tested in diabetic patients for cardiovascular safety and proved to be not only safe, but reduced the primary outcome (cardiovascular death, non-fatal heart attack or stroke), as well as cardiovascular and all-cause mortality.[49]

Lorcaserin

This drug is an agonist for the 2C serotonin receptor. Although not yet marketed in Brazil, data on its cardiovascular safety and effectiveness have recently been shown in clinical studies.[47,50-52]

Promising initial results regarding weight loss were shown in the BLOOM (*Behavioral Modification and Lorcaserin for Overweight and Obesity Management*) and BLOSSOM studies, at a dose of 10 mg compared to a placebo. Both studies showed that the drug was effective for weight loss in relation to the placebo. Approximately half of the population loss more than 5% initial body weight and approximately 1/5 of the population lost more than 10% when exposed to lorcaserin treatment.[47,50] In 2018, the results of the study CAMELLIA-TIMI 61 (*Cardiovascular and metabolic effects of lorcaserin in overweight and obese patients - thrombolysis in myocardial infarction 61*), a randomized, double-blind, placebo-controlled study that evaluated the effectiveness and cardiovascular safety of lorcaserin in 12,000 patients with high cardiovascular and metabolic risk over five years, were presented.[51,52] Major cardiovascular outcomes (cardiovascular death, acute myocardial infarction or stroke) occurred similarly between the group exposed to lorcaserin and placebo, after a median of 3.3 years.[52] Active treatment also modestly reduced blood glucose and the incidence of new cases of diabetes, and decreased blood pressure, heart rate and triglycerides. The drug was well tolerated and did not cause a significant increase in valve diseases, but an increase in hypoglycemia was noted.[52]

Naltrexone/bupropion

This combination of two central agents (8 mg naltrexone and 90 mg bupropion) is approved in the USA and Europe for the treatment of obesity. The total recommended daily dose is 32 mg of naltrexone and 360 mg of bupropion, with gradual titration every three weeks. Despite significant improvements in weight loss, adverse effects such as nausea, seizures, increased blood pressure and myocardial infarction were reported with exposure to this combination and cardiovascular safety data have not yet been fully established.[53-56]

Phentermine/topiramate

The combination of immediate-release phentermine with gradual-release topiramate in a pill constitutes another method for weight control. The dose starts with 3.75/23 mg a day and can be increased to 7.5/46 mg or 15/92 mg, respectively for phentermine/topiramate. Although effective for weight reduction and showing metabolic benefits, its cardiovascular safety has not yet been established and these drugs are not available in Brazil.[47,50,57]

Sibutramine

This drug is a serotonin and norepinephrine reuptake inhibitor that increases endogenous levels of catecholamines, promotes satiety by central actions, and determines increased energy expenditure. With these actions, although it promotes weight loss, it also increases blood pressure, heart rate and is not indicated for patients with a history of cardiovascular disease. It has been withdrawn from the market in several countries such as the USA and Europe, but is still being marketed in Brazil and some Latin American countries. The SCOUT study included over 10,000 participants and showed, after a mean exposure of three and four years, an increase in the primary cardiovascular safety outcome of the study, including an increase in myocardial infarction or stroke rates.[58]

Surgical treatment

Contemporary surgeries have evolved a lot and today can be performed using laparoscopic techniques which allow for faster recoveries and lower rates of complications and mortality.[59] These surgical procedures include Roux-en-Y bypass, sleeve gastrectomy, adjustable gastric band, and duodenal switch, but are associated with nutritional complications such as vitamin and protein deficiencies, especially with the most malabsorptive techniques. On the other hand, great benefits in metabolic disorders have also been described, including remission or reduction of hyperglycemia in patients with diabetes, decreased blood pressure, and reduced cholesterol.[59]

A condition frequently found in obese patients with indication for bariatric surgery is the concomitant and often unrecognized presence of non-alcoholic steatohepatitis or cirrhosis (NASH) in patients with non-alcoholic fatty liver disease (NAFLD). The presence of cirrhosis represents an advanced stage of liver disease with necrosis, inflammation, and fibrosis, which is associated with nodular regeneration and loss of liver architecture, development of portal hypertension, and the impairment of synthetic function.[60] The concomitance of NASH in obese patients with indication for bariatric surgery is an increasingly frequent dilemma for surgeons considering the delicate balance between the greater surgical risk and possible benefits that have been described in steatohepatitis and even cirrhosis.[61] The choice of operative technique for these patients should be individualized and preferably performed in patients with a liver disease score not higher than Child's A.[61] Finally, metabolic surgery, its indications and benefits in the prevention and treatment of diabetes deserves to be highlighted.[62]

TREATMENT OF DYSLIPIDEMIA IN OBESE PATIENTS

The lipid alterations commonly presented by obese patients can be defined as "atherogenic dyslipidemia", which is characterized by an increase in the number of small and dense LDL-C particles, low HDL-C levels and high triglycerides (TG).[63]

Atherogenic dyslipidemia is strongly associated with cardiovascular disease. This risk factor, however, is reflected very little in stratification through prediction scores and even by the dosage of LDL-C levels, which are often not very high. The best variable to identify atherogenic dyslipidemia, especially in individuals with high TG, is non-HDL cholesterol which estimates the amount of atherogenic lipoproteins circulating in the plasma.[64]

Lifestyle interventions for optimizing diet and physical activity with consequent weight loss are the basis of therapeutic guidelines for obese patients, but adequate control of atherogenic dyslipidemia will often require drug therapy to achieve the appropriate lipid goals to reduce the cardiovascular risk of this patient profile.[65]

ATHEROGENIC DYSLIPIDEMIA

Atherogenic dyslipidemia corresponds to a spectrum of qualitative lipid abnormalities, which reflect disturbances in the structure, metabolism and biological activities of lipoproteins, and are caused by insulin resistance.

First, insulin usually suppresses lipolysis in adipocytes, and thus the dysfunction of insulin signaling increases lipolysis, resulting in increased levels of free fatty acids (FFA). In the liver, the FFA serve as a substrate for TG synthesis. The FFA also stabilize the production of apolipoprotein-B (apoB), the main lipoprotein of the VLDL, resulting in greater production of VLDL.

Second, insulin usually degrades apoB through PI3K-dependent pathways, and insulin resistance directly increases VLDL production. Third, insulin regulates the activity of lipoprotein lipase, which is responsible for regulating production and being the main mediator of VLDL removal. Thus, hypertriglyceridemia in insulin resistance is a result of both increased production of VLDL and its decreased removal.

VLDLs, in turn, are metabolized into remaining lipoproteins and small, dense LDL. TGs from VLDLs are transferred to HDLs by the carrier enzyme, CETP, in exchange for cholesterol esters, resulting in TG-rich HDL and cholesterol ester-rich VLDL particles. TG-rich HDLs are the best substrates for hepatic lipase and are then rapidly removed from circulation, decreasing the amount of HDL particles participating in the reverse transport of vascular cholesterol.

Thus, in the livers of patients with insulin resistance, the flow of FFA is high, the synthesis and storage of TG is increased, and excess TG is secreted as VLDL. This increase in VLDL, a direct consequence of insulin resistance, characterizes atherogenic dyslipidemia and is associated with increased oxidative stress and endothelial dysfunction, reinforcing the pro-inflammatory pathways of atherosclerotic disease.[66]

DRUG TREATMENT

As recommended in the guidelines, once lifestyle changes are optimized and based on the individual stratified risk, which invariably includes intermediate or high 10 year cardiovascular risk, drug treatment should be indicated for obese patients with atherogenic dyslipidemia.

The initial goals of the treatment are to reduce LDL-C levels (primary goal) and non-HDL cholesterol levels (secondary goal). Statins are the drugs of choice because they represent the clinically most validated therapy for the reduction of cardiovascular events.

For patients with intermediate risk, dyslipidemia treatment aims at reductions between 30% and 50% of LDL-C levels (with LDL-C goals below 100 mg/dL and non-HDL cholesterol goals below 130 mg/dL); and for high risk patients, reductions of 50% of LDL-C (with LDL-C goals below 70 mg/dL and non-HDL cholesterol goals below 100 mg/dL) is the aim.

Statins are considered the most effective class in reducing LDL-C and have minimal interactions with other drugs and side effects that lead to treatment interruption. Depending on the dose and statin used, reductions in LDL-C may exceed 50% in relation to the baseline level, and increases between 5% and 10% in HDL-C and decreases of up to 30% in TG and 39% in VLDL-C can be achieved, with more effective statins with longer plasma half-life. The additional or pleiotropic effects of statins are implicated with very favorable effects on inflammation, endothelial function and cardiovascular events.

In patients whose LDL-C goal has not been achieved with adequate doses of statins, the association with ezetimibe may amplify the LDL-C reduction. Statins can also be safely associated with fibrates, especially fenofibrate, when non-HDL or even TG goals have not been achieved. These associations, in general, are well tolerated by patients. For patients with high TGs and low HDL, nicotinic acid, if well tolerated, may be a therapeutic option.[67]

For high-risk patients with persistently high TGs, the use of highly purified and high-dose omega-3 eicosapentaenoic acid (EPA) has been shown to reduce the risk of cardiovascular events.[68]

Thus, the treatment of dyslipidemia in obese patients is recommended in the evolution of this profile of patients, where multiple physiological, biochemical, metabolic and clinical factors are interconnected and directly related to substantial increases in the risk of diabetes, cardiovascular atherosclerotic disease, and all-cause mortality.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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