

COVID-19 Comorbidity Interplayers: Diabetes and Atherogenic Dyslipidemia

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Abstract

Diabetes mellitus is considered an important independent risk factor for coronary artery disease. Atherosclerosis is the most frequent cause of premature death in this group of patients, doubling the risk of coronary disease, tripling the risk of stroke and quadrupling the possibility of peripheral vascular insufficiency symptomatic. Coronavirus (COVID-19) diagnosed patients can do worse when comorbidities are associates. In this paper we present two of them and their interplay that can act addingly to worsen COVID-19 outcome. The two factors can interplay in this role are diabetes and hyperlipidemia. Metabolic syndrome can be a possible precursor of type 2 diabetes: the prevalence of dyslipidemia in patients with type 2 diabetes mellitus is 75%. The components of dyslipidemia in type 2 diabetes mellitus are characterized by quantitative, qualitative and kinetic alterations, all contributing to the risk of cardiovascular disease, the main cause of mortality in this population, mainly related to insulin resistance. Relatively normal cholesterol "hides" an atherogenic lipid profile, with increased intermediate density lipoproteins, small and dense LDL lipoproteins, and small, dense and dysfunctional HDLs. Lipid-lowering drugs for LDL-c have the best documented risk reduction with HMGCoA Reductase inhibitors: (statins). Other medications are: inhibitors of intestinal cholesterol absorption (Ezetimibe, Cholestryamine and Cholesevelam), nicotinic acid, fibrates (Gemfibrozil, Phenofibrate and Pemafibrate), omega 3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid) plus new drugs such as and PCSK9 inhibitors. Lifestyle changes, which include the elaboration of an adequate diet, regular practice of physical exercises and control of the common state of anxiety in a large number of patients, should be the first step in the diabetic dyslipidemia therapeutic approach. Unnecessary to emphasize that prior to the institution of lipid therapy, adequate blood glucose control should be achieved.

Keywords: Apolipoprotein B; Comorbidity; Covid-19; Diabetes Mellitus; Hypercholesterolemia; Lipoprotein remnant; Low Density Lipoprotein Cholesterol; Modified LDL

Abbreviations: Apo B: Apolipoprotein B; DM: Diabetes mellitus; DM 2: Type 2 diabetes mellitus; HDL: High Density Lipoprotein; HDL-c: High Density Lipoprotein Cholesterol; LDL: Low density lipoprotein; LDL-c: Low Density Lipoprotein Cholesterol; LDLR: Low Density Lipoprotein Receptors; VLDL: Very Low Density Lipoprotein

Introduction

Pandemic Coronavirus (COVID-19) diagnosed patients can do worse when comorbidities are associated [1-3]. According to publications based on meta-analysis demonstrated that the highest ODDS RATIO for risk increase in COVID-19 is diabetes, followed close by hypertension [4]. According to the official document released by the Brazilian Diabetes Association based on the Ministry of Health indications, the International Diabetes Federation and the American Diabetes Association there are instructions that should be incorporated by all health professionals.

Those with Diabetes Mellitus (DM) do not have a higher risk of being contaminated by coronavirus, but have a higher risk of complications from the infection. Low immunity is linked to increased blood sugar, not lack of insulin production. A person with diabetes who is very overweight may also have immunity affected by having greater inflammation. The risk of complications from COVID-19 is much lower and almost equal to that of people without diabetes if blood sugar levels are controlled. The risk of complications is higher for those aged 60 years or older, with complications of diabetes, with concomitant diseases such as high blood pressure and who have high blood sugar levels, regardless of the type of diabetes. The person who has insulin resistance but does not have diabetes is not in the risk group for complications. There is no vitamin, serum, alternative therapy or therapy said to increase immunity that prevents or treats COVID-19. There is no data available with a level of evidence that can state that prediabetic patients are at increased risk in the face of a coronavirus infection. It should be noted whether prediabetes is present in people with other associated pathologies and in the elderly. All patients, at risk or not, should follow the same general guidelines to avoid contagion and follow all the guidelines of the current health authorities. Regarding patients that are on Captopril, Enalapril, Losartan, Aspirin or Pioglitazone there are no evidences that they should be suspended and so they must carry on as prescribed by their doctors.

Emphasising, in this paper we present two of them and their interplay that can act addingly to worst COVID 19 outcome. The two factors can interplay in this role are Diabetes and Hyperlipidemia. DM is considered an important independent risk factor for coronary artery disease. Atherosclerosis is the most frequent cause of premature death in this group of patients, doubling the risk of coronary disease, tripling the risk of stroke and quadrupling the possibility of peripheral vascular insufficiency symptomatic [5]. In this paper we present two of them and their interplay that can act addingly to worst COVID 19 outcome. The two factors can interplay in this role are Diabetes and Hyperlipidemia. DM is considered an important independent risk factor for coronary artery disease. Atherosclerosis is the most frequent cause of premature death in this group of patients, doubling the risk of coronary disease, tripling the risk of stroke and quadrupling the possibility of peripheral vascular insufficiency symptomatic [5].

Regardless of age group, DM increases the risk of cardiovascular disease. In relation to women, diabetes confers a higher risk for atherosclerotic disease, even at earlier ages, similarly to those observed in males [6]. The association between atherosclerotic disease and DM can be attributed to a number of characteristics, which facilitate atherogenesis in this group of patients, such as the concomitance of other risk factors, of which obesity, hypertension levels of fibrinogen and dyslipidemias are

the most important [7,8].

Lipid changes of diabetic patients: dyslipidemias in diabetic patients may be secondary to non-fully controlled disease, or to the use of drugs (diuretics, beta-blockers, etc.) administered to associated pathologies, which unfavorably modify the lipid profile. They can still be primary when related to the genetic component. The alteration of serum lipids most common in the inadequately controlled diabetic patient is hypertriglyceridemia, often associated with hypoalphalipoproteinemia [9].

In poorly controlled insulin-dependent diabetic patients, decreased insulin levels promotes lower lipoprotein lipase activity, an enzyme responsible for triglyceride hydrolysis in free fatty acids and glycerol, thus reducing the metabolism of chylomicrons and Very Low Density Lipoprotein (VLDL). At the same time, the lack of insulin accelerates lipolysis in adipose tissue, promoting an important release of free fatty acids, which act as a substrate for the production of VLDL in the hepatocyte [10]. In non-insulin-dependent diabetics, where insulin resistance is marked, increased triglyceridemia is probably due to a higher production of VLDL by the liver, which receives greater glucose and free fatty acids as substrate [10]. Also in relation to VLDL, it was found in studies that non-insulin dependent diabetic patients, when compared to controls with normal glucose tolerance test (properly matched according to normal glucose tolerance index body mass and fasting triglyceridemia) presented higher concentrations of these lipoproteins in the postprandial period [11]. The real role of elevation of VLDL in the postprandial period in atherosclerosis is a subject of interest of researchers from various centers, being associated with atherosclerotic disease in several studies [12]. The reduction of high density lipoprotein cholesterol (HDL-c) levels in poorly controlled insulin-dependent diabetic patients is due to a lower supply of elements that form this lipoprotein, originating from the metabolism of chylomicrons and VLDL by the action of the lipoprotein lipase enzyme, which has its activity decreased with the drop in insulinemia that occurs in this group of patients [9,10].

In relation to non-insulin-dependent diabetic patients, the hypo-alphalipoproteinemia observed seems to be linked to increased activity of the hepatic lipase enzyme (implicated in HDL-c catabolism) secondary to higher insulin resistance [9,10]. Particularly in diabetic patients with renal dysfunction, there is evidence that there is a selective urinary excretion of HDL-c, further reducing their serum levels [10]. Regarding the low density lipoprotein cholesterol (LDL-c) fraction in diabetics, the differences seem to be more qualitative than quantitative. Data from the NHANES II study indicate that higher LDL-c levels are found in the group of diabetic patients than in the general population. However, this alteration has not been constant in other surveys involving patients with this disease [13].

Considering the composition of LDL-c particles, there is a high prevalence of small and denser particles in diabetic individuals, even when normolipidemic [14]. Non-enzymatic glycosylation and lipid peroxidation, which occur in greater intensity in diabetics without adequate control, provide the formation of lipoproteins respectively glycosylated and oxidized, which have greater atherogenic potential [10].

Dyslipidemias secondary to diseases and metabolic alterations: metabolic syndrome as a possible precursor of type 2 diabetes: the prevalence of dyslipidemia in patients with type 2 diabetes mellitus (DM 2) is 75%. The components of dyslipidemia in DM2 are characterized by quantitative, qualitative and kinetic alterations, all contributing to the risk of cardiovascular disease, the main cause of mortality in this population, and are mainly related to insulin resistance. The laboratory phenotype is variable, including: a) mixed dyslipidemia with elevation of plasma triglycerides; b) reduction of HDL-c; c) normal or low elevated LDL-c, with numerous small and dense particles; d) apolipoprotein B (apo B) elevated, reflecting the number of particles of the atherogenic lipoproteins VLDL and their remaining; e) Postprandial lipemia - increase of chylomicrons and their remnants.

Pathophysiology: insulin resistance associated with visceral adiposity are key factors for the development of DM 2 dyslipidemia [15]. Hypertriglyceridemia is accentuated by reduced lipoprotein lipase activity, which can be negatively regulated in states of insulin resistance or deficiency [16]. The activity of the cholesterol ester carrier enzyme is increased in diabetes, which partly explains the lipid and atherogenic potential changes present in type 1 and 2 diabetes. The increased activity of the cholesterol ester carrier enzyme will determine the transfer of cholesterol esters from other lipoproteins, mainly from High Density Lipoprotein (HDL), to VLDL. At the same time, VLDL transfer triglycerides to HDLs and Low Density Lipoprotein (LDL), depletable from cholesterol esters [17,18]. HDLs and LDLs enriched with triglycerides and with little cholesterol ester suffer the action of lipoprotein lipase and liver lipase, which transform them into small, dense, more atherogenic particles.

Small and dense LDL particles, despite carrying less cholesterol esters, are very numerous, resulting in lipid profile with normal or low LDL-c values and very high apo B, which can hide atherogenic potential [19-21]. The presence of genetic forms of

dyslipidemia, obesity, sedentary lifestyle, management of hyperglycemia, presence of complications such as nephropathy, especially in nephrotic syndrome, exacerbate diabetic dyslipidemia.

Laboratory evaluation of lipid profile in DM 2: relatively normal cholesterol "hides" an atherogenic lipid profile, with increased intermediate density lipoproteins, small and dense LDL lipoproteins, and small, dense and dysfunctional HDLs [22-24]. Each LDL particle, regardless of its density or cholesterol content, contains an apo B molecule. Normal LDL-c values associated with high apo B, reflect numerous of LDL particles, small and dense in circulation [25]. Therefore, plasma levels of apo B are markers of cardiovascular risk, more than serum LDL-c concentrations [26]. Although intensive care in Diabetes Control and Complications Trial (DCCT) has not significantly modified LDL-c and HDL-c levels, it has been associated with decreased levels of apo B and Lp(a), introducing the importance of evaluating non-traditional laboratory risk markers in diabetic patients [27].

Another way to evaluate lipoproteins rich in triglycerides is non-HDL cholesterol, without the need to dose apo B. It is easy, with low cost, can be used for segment and in the evaluation of lipid-lowering therapy in these patients. Non-HDL cholesterol is considered the best predictor of cardiovascular risk in this population [28].

Treatment: diabetic dyslipidemia is largely exacerbated by glycemic uncontrollability, inadequate diet, physical inactivity, obesity, and excessive alcohol intake. Lifestyle modifications are the first therapeutic line for diabetes dyslipidemia and include weight loss, diet and aerobic exercises.

Effects of hypoglycemic drugs on lipoproteins: dyslipidemia in DM 2 can be partly corrected by insulin treatment and glycemic control resulting in reduction of triglycerides and elevation of HDL-c [29,30]. Drugs widely used in the treatment of diabetes such as metformin, which decrease insulin resistance, also reduce hypertriglyceridemia, although it is considered only as hypoglycemic [29,31]. Other medications used to treat diabetes may have positive or negative effects on lipoproteins (Table 1). One example is the small increase in LDL-c observed with sodium-glucose cotransporter 2 - SGLT2, suggesting that the significant reduction in cardiovascular events, recently observed with empagliflozin, is not related to the effects about lipid profile [32].

Medication	Total Cholesterol	LDL-C	HDL-C	Triglycerides	References
Metformin	↓↔	↓	↔↑	↓↔	[33]
Gliclazide	↓	↔	↔	↓	[34,35]
Glimepiride	↔	↔	↔↑	↔	[34,36]
Pioglitazone	↑	↔	↑	↓	[37,38]
Sitagliptin	↔	↔	↔↑	↔	[39,40]
Saxagliptin	↔	↔	↔	↔	[35,41]
Vildagliptin	↔	↔	↔↑	↔	[42]
Linagliptin	↔	↔	↔	↔	[43]
Dapagliflozin	↔↑	↔↑	↔↑	↓↔	[44,45]
Canagliflozin	↑	↑	↑	↑	[40,46]
Empagliflozin	↔↑	↔↑	↔↑	↔	[32,47]
Exenatide	↓↔	↔↑	↔↑	↑	[38,48]
Liraglutide	↔	↔	↔	↓	[49,50]

↑ Increase, ↔ Does not change, ↓ Decrease

Table 1: Effects of hypoglycemic agents on lipoproteins.

Lipid-lowering: LDL-c is the best documented risk factor in the occurrence of cardiovascular events. The relative risk of mortality from cardiovascular disease is higher in diabetic patients than in non-diabetic patients, varying according to cholesterol values [51]. Therefore, LDL-c is a therapeutic target for reducing cardiovascular risk.

HMGCoA Reductase Inhibitors: statins are medicines of choice in the treatment of dyslipidemia of diabetic patients. Its main effect is the reduction of LDL-c, inhibiting the limiting enzyme in cholesterol synthesis, Hydroxymethylglutaryl Coenzyme Reductase - HMGCoA reductase, increased liver expression of LDL-c receptors, increased removal of LDL-c, decreasing its values plasma. Although LDL-c is not very high in diabetic dyslipidemia, statins are the most effective drugs in reducing morbidity and mortality due to cardiovascular disease in diabetic and non-diabetic populations [52,53]. Apparently, the relative risk reduction observed with statins is similar in patients with and without diabetes, however the number needed to treat (NNT) and prevent an event is lower in diabetics compared to non-diabetics [54].

The risk reduction by statins is dose-dependent, with greater risk reductions with higher doses. One in seven diabetics treated with statins will still experience a cardiovascular event in five years. Clinical trials present unequivocal evidence for the use of statins in primary and secondary diabetes prevention, however, the populations studied may not be representative of younger patients or with advanced kidney disease. These subgroups require studies,

and clinical judgment in prescription is important.

Inhibitors of intestinal cholesterol absorption: Ezetimibe is an inhibitor of the absorption of dietary and biliary cholesterol, by preventing the transport of cholesterol from the intestinal lumen into the enterocytes of the small intestine [55], resulting in a reduction of 15% to 20% of plasma cholesterol [56], without affecting the absorption of fat-soluble vitamins [57]. Ezetimibe binds to the protein "Niemann-Pick C1-Like 1", located in the brush-edge cells of the intestinal epithelium, blocking the absorption of cholesterol. The IMPROVE-IT Study evaluated 18,144 patients with an acute coronary syndrome, of whom 27% were diabetic. The group receiving simvastatin 40 mg and ezetimibe 10 mg showed reductions in the rates of combined events when compared to the group with simvastatin during a 6-year follow-up. This study demonstrated additional benefits in reducing LDL-c, corroborating the hypothesis that lower LDL-c targets should be achieved to reduce residual risk, and that additional benefits can be obtained with non-statin drugs [58]. Cholestryamine may be effective in lowering LDL-c, however, both agents may increase triglycerides and are poorly tolerated [59]. Cholesevelam, a bile acid sequestrant, can reduce glycated hemoglobin (Hb A1c), total cholesterol and LDL-c by 20% [60].

Fibrates and nicotinic acid: high concentrations of triglycerides, low HDL-c and non-HDL-high cholesterol are factors that contribute to increased residual risk in this population. Fibrates are potent drugs that reduce plasma triglycerides by 30% to 50%,

being considered as adjuvants in the treatment of persistent hypertriglyceridemias, after lifestyle modifications and statin therapy. First-choice therapy is considered for triglycerides above 500 mg/dL during fasting, minimizing the risk of pancreatitis [61,62]. They act as agonists of PPAR- α receptors (peroxisome proliferator-activated receptors), activating them, with consequent attenuation of lipid, inflammatory, and atherogenic changes [63]. These drugs decrease the concentrations of apolipoprotein C-III (apo C-III) and apolipoprotein A-V (apo A-V) and amplify the activity of lipoprotein lipase with increased intravascular lipolysis. They promote synthesis of apolipoprotein A-I (apo A-I), apolipoprotein A-II (apo A-II), SREBP1 receptor and ABCA1 transporter, in addition to increasing reverse cholesterol transport and increasing HDL-c concentrations [63].

Fibrates are generally well tolerated, although the risk of muscle toxicity increases when combined with statins, and associations of certain fibrates such as gemfibrozil with statins are outlawed [64]. The VA HIT (Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group) study used gemfibrozil versus placebo in secondary prevention patients, and a 24% reduction in combined events was observed. Statins were not available when this study was conceived [65].

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9.795 subjects with DM 2 were randomized to receive micronized phenofibrate or placebo [66]. There was an 11% reduction in combined events in the fenofibrate group compared to placebo. The use of statins was a considerable confounding factor in the placebo group, which may have influenced the result. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study evaluated the impact of the combination of fenofibrate in type 2 and high-risk diabetic patients who already used statins on cardiovascular outcomes. There was no benefit of the association of fibrates with statins in reducing risk, except in the subgroup of patients with high triglyceride concentrations and low HDL-c levels. The same was observed in the FIELD study, with reduction of outcomes in the subgroup with elevated triglycerides and low HDL-c [67]. Based on these results, meta-analysis observed an additional risk reduction with the use of fibrates, associated or not with statins, in patients with triglycerides above 204 mg/dL and HDL-c below 34 mg/dL [68].

Pemafibrate (K-877) is a new selective modulator of PPAR α receptors, and when compared to fibrates, it is more effective in reducing triglycerides and increasing HDL-c, without presenting adverse effects of fibrates such as increases in homocysteine and plasma creatinine [69]. A phase 2 clinical trial with pemafibrate in patients with atherogenic dyslipidemia revealed a significant reduction in triglycerides and increased HDL-c, with rates comparable to adverse events to placebo, such as serum creatinine and increased liver enzymes, suggesting that pemafibrate may have a better benefit/risk balance than fenofibrate [70]. The PROMI-

NENT study (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) (clinicaltrials.gov identifier: NCT03071692) is a multicenter study with 10.000 patients that will evaluate cardiovascular outcomes patients using pemafibrate versus placebo [71].

Nicotinic acid or niacin is a soluble vitamin with lipid-lowering action: it reduces triglyceride levels (20-50%), LDL-c (5-25%) and increases HDL-c (15-35%). The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) and HPS2-THRIVE (Heart Protection Study) have shown no benefits, in addition to increased adverse effects with the combination of long-acting niacin and laropiprant statins in patients with atherosclerotic and metabolic syndrome disease being withdrawn from the market. Today there is only rapid-release niacin, which has limited use by side effects and lack of evidence of benefits.

Omega 3 fatty acids: Omega-3 fatty acids of marine origin such as docosaeaxenoic acid (DHA) and eicosapentaenoic acid (EPA) exert numerous cardiovascular effects, and regular consumption of omega-3-rich fish are part of a healthy diet. Despite the benefits, evidence is conflicting in recommending dietary supplementation of fish oil capsules for cardiovascular prevention. Studies show that supplementation with 2 to 4 g of EPA/DHA per day reduces triglyceride levels by 25% to 30%, increases HDL-c by 1% to 3% and LDL-c by 5% to 10% [72,73]. Other benefits include anti-inflammatory and antiarrhythmic effects, improved endothelial function, effects on sudden death, and cardiovascular outcomes. Studies with EPA supplementation and DHA had a small or zero effect on cardiovascular mortality (evidence of moderate quality). Poor-quality evidence suggests that the supplementation reduces cardiovascular events, including cardiovascular mortality and arrhythmia [74].

Recently, the REDUCE IT trial (Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia) study evaluated patients with established coronary artery disease or diabetes, using statins, randomized to receive 4 gr of purified EPA for 4.9 years. There was a 25% reduction in risk for primary outcomes that included cardiovascular death, non-fatal infarction, non-fatal stroke, myocardial revascularization and unstable angina [75]. This study may modify clinical practice in the cardiovascular prevention of very high-risk patients and diabetics, who maintain high residual risk. Our orientation is in accordance with the American Diabetes Association - ADA recommendations [76].

New drugs: The most recent advance in cholesterol reduction therapy was the discovery of anti-PCSK9 antibodies (protein convertase subtilisin/kexin type 9). They reduce LDL-c to unprecedented levels, especially when used in combination with statins and/or ezetimibe.

Mechanism of action: the PCSK9 protein is synthesized in the liver and in a smaller amount in the intestine, brain and pancreas. It has a determining role in plasma LDL-c concentrations, as it regulates the hepatic expression of low density lipoprotein receptors (LDLR). After being secreted by hepatocytes, PCSK9 binds to the LDLR liver receptor, being internalized together with the receptor complex and lipoprotein within lysosomes, having its content degraded, preventing the recirculation of LDLR to the surface liver. The lower density of these receptors results in lower removal of LDL particles, increasing the plasma values of this lipoprotein [77].

Therapeutic inhibition of circulating PCSK9 by anti-PCSK9 monoclonal antibodies increases the density of LDLR on the cell surface and the removal of LDL particles, reducing LDL-c levels in plasma. PCSK9 inhibitors are complementary to statin therapy in reducing cholesterol. In a pre-specified analysis of the study "Alirocumab and Cardiovascular Outcomes in Patients with Acute Coronary Syndrome (ACS) and Diabetes - Prespecified Analyses of ODYSSEY OUTCOMES", benefits were demonstrated in the diabetic population [78].

It was a randomized study that evaluated in 18,924 patients with acute coronary syndrome and baseline LDL levels above 70 mg/dL, the use of alirocumab associated with statins at maximum tolerated doses versus statin and/or ezetimibe, for 2 and a half years. The recommended LDL-c target was 25-50 mg/dL.

The alirocumab group significantly reduced Major Adverse Cardiac Events (MACE) - death from coronary heart disease, fatal and non-fatal myocardial infarction (IM), fatal and non-fatal ischemic stroke, or hospitalization for angina compared to the group with statins. In a pre-specified analysis, 28.8% had diabetes, 43.6% had prediabetes and 27.7% had normal glucose levels. Patients with diabetes in the alirocumab group had the highest reduction in absolute risk (2.3%), almost double the reduction when compared to prediabetics (ARR of 1.2%) and non-diabetics (ARR of 1.2%), most likely due to the high absolute risk of events in the population of diabetics with acute coronary syndrome.

The FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) clinical trial was a randomized study for evolocumab (140 mg every 2 weeks or 420 mg once a month) versus placebo, including 27,564 patients with ages 40-85 years, with clinical atherosclerotic cardiovascular disease (previous myocardial infarction, non-hemorrhagic infarction, stroke or symptomatic peripheral arterial disease) and additional risk factors (including diabetes), with 2.2 years, and significant reduction in cardiovascular events [79].

In a pre-specified analysis of the diabetic subgroup, 40% had diabetes, 60% did not. The mean reduction of LDL-c was 57% in diabetics and 60% in non-diabetics. As patients with diabetes

had a higher risk at the beginning of the study, this group tended to reduce the absolute risk [79]. These drugs are recommended in guidelines, associated with statins at maximum doses, to achieve more aggressive goals in very high-risk patients.

As last conclusions: adequate glycemic control of diabetic patients, through pharmacological or non-pharmacological measures, may normalize the lipid profile.

Non-pharmacological treatment: lifestyle changes, which include the elaboration of an adequate diet, regular practice of physical exercises and control of the common state of anxiety in a large number of patients, should be the first step in the diabetic's therapeutic approach dyslipidemic. The diet should be elaborated individually, considering the preferences and socioeconomic conditions of the patient. Overweight should be fought. The total calories ingested should be sufficient for the optimal weight to be maintained or achieved.

The adequate distribution in the carbohydrate and fat diet facilitates the achievement of more favorable results in relation to blood glucose and lipid profile. Simple carbohydrates should be replaced by complexes, representing 50% to 55% of the calories to be ingested per day. The total percentage of fats should not exceed 30%, and saturated fat content should be less than 10%. Cholesterol intake should not exceed 300 mg/day. Greater restrictions can be performed on the dependence on the need for each case [80,81]. The consumption of soluble fibers (35 to 40 g/day) should be encouraged, as its intake decreases post prandial glycemia, fasting triglyceridemia and prandial powders and serum cholesterol [82]. Alcohol abuse should be avoided both by the possibility of elevating triglyceridemia, and by creating more favorable conditions for liver dysfunction. Regular physical exercise practice provides an increase in glucose uptake and reduces insulin resistance, facilitating glycemic control. Improves lipid profile by reducing triglyceridemia and increasing HDL-c levels [83,84].

Pharmacological treatment: prior to the institution of lipid therapy, adequate blood glucose control should be achieved. The treatment of DM, both with insulin and with oral hypoglycemic patients, can also favorably modify the lipid profile. After insulin administration and elevation of its serum levels, lipoprotein lipase activity normalization occurs, improving the catabolism of VLDL and subsequent HDL-c formation. In relation to oral hypoglycemic users, it is verified that, among biguanides, metformin promotes in parallel the decrease in glycemia, a reduction in VLDL levels, improving the lipidic profile.

As long as normalization of serum lipids is not achieved after non-pharmacological measures and adequate blood glucose control have been excluded and other secondary causes of dyslipidemia have been ruled out, the administration of hypolipidemic drugs is indicated [85]. Statins are the drugs of choice in cases of isolated

elevations of LDL-c levels. For isolated hypertriglyceridemias and mixed dyslipidemias, fibrates should be used initially. The use of bile acid sequestering resins should be avoided by the possibility of increasing triglyceridemia and nicotinic acid by increasing insulin resistance [86].

Conclusion

If the ideal values of lipids are not reached, the association of drugs should be considered. In patients with hypertriglyceridemia, important even in the presence of a full dose of one of the drugs in the fibrate group, the association of a statin may be beneficial. Anamnesis and periodic evaluation of transaminases and creatinophosphokinase identify, respectively, the rare cases of hepatitis and rhabdomyolysis secondary to this combination of medicines.

The use of antioxidants, although logical, as it would decrease the formation of lipoproteins in the oxidized form, has not yet been ratified in prospective long-term studies. In conclusion, the therapy of dyslipidemic diabetic patients should be aggressive, being directed in order to correct the metabolic alterations found according to the respective cardiovascular risk through lifestyle modifications and medicines. Once reached this goal these patients can respond to an infection as in the case of the frightening pandemic COVID19 with a better immune defence.

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Conflicts of Interest: None.

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