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Review Article: Diabetes as secondary cause in Hyperlipidemia

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ABSTRACT
It has long been known that the most common lipoprotein alteration among diabetic patients is hypertriglyceridemia. Plasma triglyceride elevation is directly related to decreased lipoprotein lipase activity. Mixed dyslipidemias are also common in diabetic individuals. It is worth calling attention to the abnormalities related to low-density lipoprotein cholesterol (LDL-c) particles. The treatment of dyslipidemia in diabetic individuals begins with measures aimed at adequate control of the underlying disease. Normalization of glycemic levels is often sufficient to correct Iipid changes. Diabetes control involves some non-pharmacological measures that are common to the treatment of dyslipidemias: diet and physical exercise (both related to the improvement in insulin resistance). Dietary guidance aims to adjust the daily caloric intake, so that the individual reaches and/or maintains adequate weight, and changes in the distribution of carbohydrates, proteins and fats in the diet, in order to provide satisfactory control of glycemic and lipid levels. Therefore, the introduction or adjustment of previous doses of oral hypoglycemic agents or insulin is necessary. If lipid levels remain high after adequate glycemic control and adherence to the proposed lifestyle modifications (diet, regular physical exercise...), we must rule out other causes of secondary dyslipidemia before indicating lipid-lowering drugs. The most commonly used medications in diabetic individuals are HMG-CoA reductase inhibitors and fibric acid derivatives.

Keywords
Diabetes, Hyperlipidemia, Triglycerides treatment, Lifestyle

Introduction

The importance of diagnosing and treating secondary dyslipidemias is related not only to the atherogenic risk they provide, but mainly to the fact that their control is often linked to the stabilization of the underlying disease/cause [1].

Diabetes mellitus is among the leading causes of secondary dyslipidemia. The prevalence of this chronic pathology has been progressively increasing in developed countries. In Brazil, the prevalence of diabetes mellitus is also high [2].

Cardiovascular diseases represent the leading cause of death among diabetic individuals [3,4]. It is already well established that lipoprotein alterations, frequent in these patients, especially in those with unsatisfactory control, contribute to the occurrence of atherosclerotic manifestations, often early [5].

Pathophysiology of lipid changes in diabetes

It has long been known that the most common lipoprotein alteration among diabetic patients is hypertriglyceridemia [6,7].

Plasma triglyceride elevation is directly related to decreased lipoprotein lipase activity. This enzyme is responsible for the hydrolysis of triglycerides into fatty acids and glycerol, and its action is linked to circulating insulin levels. Therefore, both in insulin-dependent diabetes mellitus (IDDM), in which there is a decrease in insulin levels (pancreatic b cells are unable to respond to any insulinogenic stimulus), and in non-insulin-dependent diabetes mellitus (NIDDM), in which there is an increase in insulin resistance (pancreatic b cells are unable to promote compensatory hyperinsulinemia capable of overcoming the present resistance), there is a decrease in the clearance of triglyceride-rich lipoproteins that depend on this enzyme for their catabolization (very low-density lipoprotein - VLDL and chylomicrons) [8].

More recent studies have focused attention on possible postprandial abnormalities in triglyceride-rich particles. Chen et al. compared the postprandial increase in triglyceride-rich lipoproteins between patients with NIDDM and non-diabetic controls, appropriately matched according to age, sex, body mass index, and plasma triglyceride levels. Retinylpalmitate was used to screen the postprandial plasma concentration of lipoproteins (secreted by the intestine in response to feeding). The authors demonstrated that individuals with NIDDM had higher concentrations of retinyl palmitate and that these were inversely correlated with high-density lipoprotein cholesterol (HDL-c) levels [9]. This data is extremely important, as many studies have associated postprandial plasma concentrations of triglycerides and coronary artery disease [10,11]. Patsch et al. have suggested that elevation of these concentrations represents an independent risk for coronary artery disease [12].

The decrease in HDL-c levels in diabetic individuals, especially those with NIDDM, has been shown to be as common as the increase in triglyceride levels [3]. Among the mechanisms involved is a reduction in HDL synthesis, since part of it occurs through the catabolism of chylomicrons and VLDL [13]. In NIDDM, because there is greater activity of hepatic triglyceride lipase, there is an increase in the clearance of HDL particles. A recent study demonstrating an increase in the selective urinary excretion of HDL in individuals with NIDDM may explain, in part, the reduction of these particles, especially in those with renal dysfunction [8].

Mixed dyslipidemias are also common in diabetic individuals. It is worth calling attention to the abnormalities related to low-density lipoprotein cholesterol (LDL-c) particles. First, we would like to make some considerations about the elevation of LDL levels in diabetic individuals.

Although data from the National Health and Nutrition Survey II (NHANES II) [14] indicate that LDL-c levels > 160 mg/dl occur more frequently in patients with NIDDM compared to the general population, the elevation of LDL-c levels has not been consistently demonstrated in studies involving diabetic patients [3]. Among the possible explanations for this, we have racial differences. Cowie et al. [15] showed that the increase in LDL levels occurs more frequently in white diabetics than in blacks. Another possible explanation lies in the limitation of the estimation of LDL levels calculated from Friedewald's formula [16].

The difference between measured and calculated LDL values is greater among diabetic individuals than in the general population. This is due to the altered composition of VLDL in diabetics, which makes its estimate from Friedewald's formula (20% triglycerides) inaccurate [17].

Regarding the composition of LDL-c, the prevalence of small dense particles in normolipemic diabetic individuals is noteworthy [18]. It is worth mentioning that in women the effects of diabetes and hyperglycemia on the size and density of these lipoproteins are even more pronounced [19].

The importance of the presence of small, dense LDL particles lies in the fact that they are more atherogenic and are related to a higher risk for the development of coronary artery disease [20].

The higher atherogenicity of LDL-c particles in diabetic patients also occurs due to the process of non-enzymatic glycosylation and increased peroxidation, especially in individuals with inadequate cholesterol control [8].

It is worth remembering that the increase in insulin (hyperinsulinemia), as a growth factor, leads to the proliferation of smooth muscle cells and the facilitation of the entry of lipids into these cells and into macrophages that precede the formation of the foamy cell (precursor of atheromatous plaque).

Treatment of dyslipidemia in diabetes mellitus

Before starting the discussion about dyslipidemic therapy itself, it is necessary to emphasize that in normolipemic diabetic patients, the lipid profile should be performed annually. Our goal, according to the American Diabetes Association (ADA), is to maintain LDL levels < 100 mg/dl and triglyceride levels < 150 mg/dl [21]. The treatment of dyslipidemia in diabetic individuals begins with measures aimed at adequate control of the underlying disease. Normalization of glycemic levels is often sufficient to correct lipid changes.

Diabetes control involves some non-pharmacological measures that are common to the treatment of dyslipidemias: diet and physical exercise (both related to the improvement in insulin resistance) [22-24].

Dietary guidance aims to adjust the daily caloric intake, so that the individual reaches and/or maintains adequate weight, and changes in the distribution of carbohydrates, proteins and fats in the diet, in order to provide satisfactory control of glycemic and lipid levels. Simple carbohydrates should be replaced by complex ones and fat intake should be restricted. The adoption of fiber is an important measure; its intake lowers postprandial glycemia, by slowing intestinal absorption, and reduces serum cholesterol levels by 3% to 5%. We remind you that its introduction into the diet should be carried out gradually, until it reaches about 35 to 40 g/day.

Exercises, in addition to contributing to weight control, provide an increase in glucose uptake. The cardiovascular benefits of these measures have been well described in multiple clinical trials.

Although smoking is not directly related to diabetes control, it aggravates micro and macrovascular disease. Smoking diabetics have been reported to have twice as much mortality from cardiovascular disease when compared to non-smokers [25].

Often, lifestyle changes are not enough to achieve adequate glycemic control. Therefore, the introduction or adjustment of previous doses of oral hypoglycemic agents or insulin is necessary.

If lipid levels remain high after adequate glycemic control and adherence to the proposed lifestyle modifications (diet, regular physical exercise...), we must rule out other causes of secondary dyslipidemia before indicating lipid-lowering drugs.

The most commonly used medications in diabetic individuals are HMG-CoA reductase inhibitors and fibric acid derivatives.

We should avoid the use of nicotinic acid (interferes with the carbohydrate mechanism, which can lead to hyperglycemia) and bile acid sequestrants (can precipitate a chylomicronemia syndrome), so they should not be used in patients with hypertriglyceridemia.

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Conflict of interest None.

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