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Review Article

**DYSLIPIDEMIA IN DIABETES MELLITUS TYPE 2;
PREVALENCE, PATHOPHYSIOLOGY, MANAGEMENT, AND
TREATMENT**

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Abstract:

Introduction: Recently, the incidence of diabetes mellitus type 2 has been significantly increasing in most parts of the world, with some reports estimating and overall 592 million diabetics in the year 2035.

Aim of work: In this review, we will review most recent medical literature on dyslipidemia in diabetes mellitus type 2 to discuss prevalence, pathophysiology, management, and treatment of dyslipidemia in these patients.

Methodology: We did a systematic search for dyslipidemia in diabetes mellitus type 2 using PubMed and Google Scholar search engines. The terms used in the search were: dyslipidemia, metabolic syndrome, diabetes mellitus type 2, prevalence, management, treatment.

Conclusions: Diabetes mellitus type 2 is well known to be associated with severe dyslipidemia along with endothelial damage which will lead to the development of atherosclerosis and associated cardiovascular events. Therefore, diabetic patients must control dyslipidemia in order to decrease their risk of developing atherosclerotic cardiovascular events. The first and initial step in preventing and managing dyslipidemia in diabetic patients, and patients with metabolic syndrome in general is the application of major changes in lifestyle. When lifestyle modifications fail in sufficiently controlling dyslipidemia, pharmacological agents can be considered. Pharmacological agents should also be considered in patients with relatively high risk of developing atherosclerotic cardiovascular changes within the next ten years. The first choice of antilipidemic drugs is statin.

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INTRODUCTION:

Recently, the incidence of diabetes mellitus type 2 has been significantly increasing in most parts of the world, with some reports estimating an overall 592 million diabetics in the year 2035 [1]. Currently, about 350 million individuals around the world are diagnosed with diabetes mellitus type 2, and is estimated to increase by 20% and 69% in developed and developing countries, respectively, before the year 2030 [2].

This significant increase in diabetes incidence and prevalence around the world has been associated with significant burden on both individuals and the society. Quality of life of diabetic patients is significantly worse than normal individuals, mostly due to the complications and mortality associated with diabetes. In fact, diabetic patients are known to have a significant increase in the risk of cardiovascular morbidities and mortality when compared to the general population, and this is considered the most common cause of death for most diabetic patients [3]. Moreover, diabetes mellitus type 2 has been linked to up to 6-year decrease in the overall survival of patients, which is mostly attributed to cardiovascular effects of diabetes. Reports have suggested that diabetic patients can have more than double the risk of developing cardiovascular diseases when compared to the general population. This higher risk of cardiovascular diseases in diabetic patients can be attributed to many factors, with dyslipidemia and metabolic syndrome being among the most important. In fact, both dyslipidemia and metabolic syndrome associated with diabetes mellitus have been strongly linked with atherogenic dyslipidemia, increased levels of triglycerides, increased levels of low-density lipoproteins, and increased levels of and low high-density lipoproteins. Some studies have attempted the correction of these dyslipidemias in diabetics using statins, fibrates, and niacin. However, results have not been promising [4].

In this review, we will review most recent medical literature on dyslipidemia in diabetes mellitus type 2 to discuss prevalence, pathophysiology, management, and treatment of dyslipidemia in these patients.

METHODOLOGY:

We did a systematic search for dyslipidemia in diabetes mellitus type 2 using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). Our search also looked for prevalence, pathophysiology, and management. All relevant studies were retrieved

and discussed. We only included full articles.

The terms used in the search were: dyslipidemia, metabolic syndrome, diabetes mellitus type 2, prevalence, management, treatment.

Prevalence of dyslipidemia in diabetes mellitus type 2:

Both dyslipidemias and metabolic syndrome are considered to be very prevalent in patients diagnosed with diabetes mellitus type 2, with a prevalence that differs among populations, and according to different risk factors. In addition, the variations in the definition of metabolic syndrome and dyslipidemia leads to variations in the prevalence. A recent study has reported that more than 38% of diabetic patients had triglycerides levels higher than 1.7 mmol/L, and HDL levels lower than 1.03 mmol/L [5]. Another Swedish population study reported nearly similar prevalence of dyslipidemia in more than 75 thousands participants with diabetes mellitus type 2 [6].

Dysregulation of triglyceride synthesis in type 2 diabetes

Normally, the hemostasis of hepatic lipid content is regulated by maintaining the balance between importing and exporting lipids from the hepatocytes. Any failure in obtaining this balance will result in the development of fatty liver disease, which reflects lipid accumulation in hepatocytes [7]. Several studies have examined VLDL synthesis and secretion in hepatocytes and found that insulin plays an essential role in the hemostasis of these particles [8]. In addition, de-novo lipogenesis, remnant cholesterol particles uptake, and free fatty acids esterification are all effected by insulin levels [8]. Therefore, development of insulin insensitivity in cases of diabetes mellitus type 2 will lead to dysregulation of all these previously mentioned mechanisms. In addition, free fatty acids levels and total adipose tissue volume have been found to be significantly higher in obese individuals and patients with diabetes mellitus type 2.

De novo lipogenesis, which also plays a significant role in increased triglycerides in hepatocytes, has been found to be dysregulated in patients with diabetes mellitus type 2, and insulin resistance in general [9]. This discovery led to the assessment of agents that target de novo lipogenesis in the management of diabetes mellitus type 2 and the associated fatty liver disease [10].

All these previous abnormalities will work with endothelial dysfunctions in patients who have

diabetes mellitus type 2 and will lead to the occurrence of vasculitis and possibly atherosclerosis. Generally, patients with diabetes mellitus type 2 suffer from abnormal permeability of vessels, which will lead to pathological interaction between leukocytes and endothelial cells, along with aggregation of platelets. These abnormal interactions are considered a results of decreased insulin sensitivity and hypertension and will add up to develop atherosclerosis [10].

Management of Dyslipidemia in patients with Diabetes mellitus type 2:

As previously mentioned, patients with diabetes mellitus type 2 will develop significant dyslipidemia which will lead to an increase in their risk of developing cardiovascular morbidities. Therefore, to decrease cardiovascular morbidity and mortality in diabetic patients, it is crucial to address dyslipidemia. Additionally, it is also beneficial to strictly control blood pressure and blood glucose to prevent the development of further dyslipidemia.

Dyslipidemia management in these patients can be achieved with both pharmacological and non-pharmacological interventions. It is important to know that these interventions should be applied for long periods to achieve desired results and to prevent dyslipidemia recurrence. Long-term compliance to these interventions has been proven to improve insulin resistance and atherosclerosis, and to decrease the long-term risk of cardiovascular morbidity and mortality.

Drugs and agents that have been used to target dyslipidemia are many, with statins considered to be the most important of them. Agents other than statins have been recently developed and experimented to improve blood pressure, weight, and blood pressure, along with dyslipidemia. However, to date, no drug has been successful in completely preventing or reversing mechanisms that decrease insulin sensitivity, harm endothelial tissue, and lead to vasculitis.

In the following sections of this paper, we will thoroughly discuss these interventions and evidence present on them for the management of dyslipidemia.

Lifestyle Modifications for Dyslipidemia Treatment:

Most studies have concluded that the best initial step when managing diabetic patients with dyslipidemia is to encourage lifestyle modifications, exercise, and weight loss. These simple modifications in lifestyle have been shown to significantly decrease resistance

against insulin, decrease obesity, and recover the function of endothelial tissue. In a previous observational study that included over five thousand individuals aged between 18-30 years and followed them for fifteen years, a higher body mass index was found to be correlated with higher incidence of later developing dyslipidemia and metabolic syndrome, when compared to lower body mass index [11].

General recommendations state that to improve dyslipidemia in an obese diabetic patient, a diet that contains 1000 kcal less than their usual requirements can lead to a loss of ½ kg per week [12]. Application of this diet restrictions along with regular sufficient physical activity has been found to cause about 10% weight loss in a period of six months in diabetic obese patients. Generally, a loss of 10% of weight within 12 months is considered acceptable and will lead to significant improvements [13].

Many diet modifications have been studied and assessed in attempts to improve dyslipidemia in diabetic patients. Recommendations from the Dietary Guidelines for Americans state that it is preferred to maintain good balance between intake and requirements of energy, which will keep body weight normal and acceptable. It is generally acceptable that normal diet consists of carbohydrates (about 50%), protein (about 20%), and fat (about 30%). Reduction of sodium consumption, trans fatty acids, saturated fatty acids, sweeteners, and refined grains is also recommended. On the other hand, the consumption of vegetables, fruits, peas, whole grains, legumes, nuts, dairy products, and seafood are all recommended to in a healthy diet [14].

Studies have shown that following a Mediterranean diet that has more vegetables, fruits, olive oil, and whole grains was correlated with a better more healthy lipid profile along with improved insulin sensitivity when compared to diets with low-fat content¹⁵. No sufficient evidence is present on regimens that consist of low carbohydrates levels and high protein content. Some suggest that nutrition with small glycemic index can be healthy. In general, a moderate balance diet is mostly preferred to allow for normal living activities and exercise of at least thirty minutes per day, which is preferred to be of moderate intensity [15]. In fact, evidence is redundant on the ability of this diet with exercise to prevent and treat dyslipidemia in many diabetic patients. A study of more than 3000 obese patients with normal blood pressure showed that intensive application of previously mentioned lifestyle modifications was associated with less risk of metabolic syndrome and dyslipidemia than placebo, metformin, or troglitazone

therapy. These benefits of exercise have been hypothesized to be a result of its ability to decrease the volume of adipose tissue in the abdomen [16].

Anti-Lipemic Therapy

The reduction in cholesterol levels in the blood will lead to a significant reduction in the risk of developing atherosclerosis in diabetic patients, with a dose-dependent effect. Several hypotheses have been suggested to explain this effect. Previous studies have found that pharmacological agents can play an essential role in decreasing cholesterol levels and managing dyslipidemia. Controlled trials that involved more than 100,000 patients have been successful in proving the effects of statins (along with other agents) in decreasing the impact of cholesterol on atherosclerosis and its associated morbidity and mortality [17]. A more recent meta-analysis that compared to use of mild treatment of statins with the use of intensive treatment with statins in improving and decreasing atherosclerosis risk and its associated cardiovascular complications. This study has concluded that increasing the control of dyslipidemia was significantly associated with higher improvement in atherosclerosis. Therefore, the main target in treating diabetic patients with dyslipidemia became targeting LDL cholesterol, with considering HDL and triglycerides secondary goals [18].

General guidelines recommend that for any adult who is older than twenty years, a lipid profile must be done at least once in five years. This lipid profile must assess at least the levels of cholesterol (total), and HDL cholesterol. In susceptible individuals, or individuals who show changes in their cardiac risk factors, this assessment should be done more often. For example, individuals who gain weight, or have a relative who suffered from a premature cardiovascular event, should re-do their lipid profile to follow up and re-estimate their risk of developing atherosclerosis and cardiovascular complications. In any individual who has a risk of developing atherosclerotic disease, strict control of cholesterol levels is essential. Previously, most regimens targeted the reduction of LDL cholesterol. However, more recent guidelines have suggested the additional targeting of IDL, and VLDL cholesterol levels, along with chylomicron remnants [18].

Generally, for any diabetic patient with atherosclerosis, and a risk of developing a cardiovascular event within the next ten years, statins are indicated to decrease LDL levels. Additional risk factors that further increase the risk of having a cardiovascular event include having severe elevation in cholesterol levels or a chronic kidney disease. The

target goals in these patients include having LDL levels that are lower than 100 mg/dL in moderate-risk patients, and lower than 70 mg/dL in high-risk patients. These numbers have been set based on previous observational studies that showed a significant decrease in atherosclerosis and cardiovascular events when these limits were reached [19].

In most patients, and unless there is an absolute contraindication, the first choice in treating dyslipidemia is statin (given in moderate or high intensity). The choice between moderate or high intensity treatment regimen depends on the patient's risk of atherosclerotic cardiovascular event. Some patient who receive statins therapy can have significant decline in their LDL cholesterol levels that can be as low as 40 mg/dL. This extremely low LDL level has not been shown to lead to any harm, making it preferred to continue statin treatment especially in diabetic patients with high risk of atherosclerotic cardiovascular events [19].

When treating a diabetic patient younger than 75 years, high-dose statin therapy is recommended, given no contraindication is present. In individuals who are susceptible to developing statin-related side effects, moderate-dose of statins is recommended, given the patient can tolerate it. When managing dyslipidemia in diabetic patients older than 75 years, high-dose statins therapy has not been found to lead to better outcomes than moderate-dose statin therapy. Therefore, moderate-intensity therapy is recommended in this population, with exceptions that can be made on a case by case basis [20].

In addition, young adults (older than 21 years) who have hereditary high cholesterol levels are recommended to receive high-dose statin therapy, which will improve their LDL levels and decrease their risk of developing an atherosclerotic cardiovascular event [20]. In these individuals, it is also recommended to co-administrate non-statin agents to control cholesterol levels and achieve desired LDL levels. Moreover, screening of other members of the family is also essential to early detect present dyslipidemias and control them [20].

Lipid Lowering Therapy Beyond Statins:

In diabetic patients with severe increase in triglycerides levels that reach more than 500 mg/dL, it is important to correct this as this elevation in triglycerides levels can induce pancreatitis. In these patients, combination therapy may be considered as statins alone will not be able to sufficiently improve dyslipidemia. However, most studies have not shown

significant improvements with these combination therapies like statins with fibrates or statins with niacin [20].

Large epidemiologic studies have demonstrated that high HDL levels are correlated with less risk of atherosclerotic cardiovascular events, which led to the assumption that pharmacological agents that increase HDL levels will improve dyslipidemia and decrease risk of cardiovascular events in diabetic patients, and patients with metabolic syndrome in general. This effect of HDL has been hypothesized to be due to the protective effects of HDL against endothelial injury along with its antioxidation effects and antiplatelets activity. However, these mechanisms are still not well understood and require further studies. Randomized clinical trials that studied on HDL increasing agents (like niacin) have not been successful in showing improved survival of patients. Moreover, cardiovascular mortality, rates of myocardial infarctions, and rates of strokes have also been shown not to improve following niacin treatment [21].

Some researchers have suggested targeting apolipoprotein B in the treatment of dyslipidemia in diabetics, especially those with low HDL levels or high triglycerides levels [22]. However, no solid evidence is present to determine the effects of improving apolipoprotein B levels in dyslipidemia in diabetes.

Newer Lipid Lowering Agents:

More recent lipid lowering agents include alirocumab (also known as praluent) which was approved by the FDA in 2015 for the use of dyslipidemia. This drug is a monoclonal antibody that acts by inhibiting the proprotein convertase subtilisin/kexin type 9, which is a member of the subtilases family and plays an important role in the metabolism of lipids. This drug, thus, will lead to improved destruction of LDL receptors, regulation of transport of cholesterol, and synthesis of apolipoprotein B. Statins had previously been shown to increase PCSK9 expression, which will have negative effects of dyslipidemia. Therefore, the use of alirocumab has been recommended with statins to inhibit PCSK9 and decrease LDL cholesterol levels [23].

Alirocumab is best administrated twice a month through the subcutaneous route. It has been shown in a randomized trial (that includes more than two thousand individuals with risk of atherosclerotic cardiovascular event) to significantly improve LDL levels when used in combination with statins²³. However, no evidence is present on this drug in

diabetic patients, and on its effects on diabetic dyslipidemia. Therefore, further large studies are needed to establish its effects in this subpopulation.

CONCLUSIONS:

Diabetes mellitus type 2 incidence and prevalence have been significantly increasing worldwide, which have led to significant burden on both individuals and the society. Diabetes can be associated with severe significant long-term morbidities and mortality, which can be largely prevented when well-controlled. Complications of diabetes can affect most body organs including the cardiovascular system, the central nervous system, and the renal system. Diabetes mellitus type 2 is well known to be associated with severe dyslipidemia along with endothelial damage which will lead to the development of atherosclerosis and associated cardiovascular events. In fact, patients with diabetes mellitus type 2 have more than double the risk of developing atherosclerotic cardiovascular events when compared to the general population. Therefore, along with controlling blood glucose, diabetic patients must also control dyslipidemia in order to decrease their risk of developing atherosclerotic cardiovascular events. The first and initial step in preventing and managing dyslipidemia in diabetic patients, and patients with metabolic syndrome in general is the application of major changes in lifestyle. These include changes in diet along with physical exercise and weight loss. When lifestyle modifications fail in sufficiently controlling dyslipidemia, pharmacological agents can be considered. Pharmacological agents should also be considered in patients with relatively high risk of developing atherosclerotic cardiovascular changes within the next ten years. The first choice of antilipidemic drugs is statin.

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