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COMORBIDITIES AND THEIR INTERACTIONS IN DIABETES AND ATHEROSCLEROTIC DYSLIPIDEMIA (COVID-19)

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Abstract:

In addition to high blood pressure and smoking, the onset of coronary artery disease is strongly linked to diabetes mellitus. For this population, atherosclerosis is a major killer since it increases the likelihood of developing heart disease, stroke, and peripheral vascular insufficiency symptoms by a factor of two to four, respectively. Patients with a diagnosis of coronavirus (COVID-19) may fare poorly if they also suffer from co-occurring conditions. In this study, we highlight two such factors and their interactive effects on one another that may have a multiplicative effect on the result of COVID-19. Diabetes and high cholesterol levels may play off of one other in this way. The patients having type 2 diabetes mellitus, the prevalence of dyslipidemia, which is a component of metabolic syndrome, is significantly higher at 75%. Patients diagnosed with type 2 diabetes mellitus who have variations in the quantitative, qualitative, and kinetic components of dyslipidemia are exposed to the risk of emerging insulin resistance and dying from cardiovascular disease. There is a "hidden" atherogenic lipid profile that can be found when there are high amounts of intermediate-density lipoproteins, small and dense low-density lipoproteins, and small, dense and dysfunctional high-density lipoproteins. This profile can hide otherwise normal cholesterol levels. HMGCoAredutase inhibitors, a class of lipid-reducing medications, have the largest body of evidence showing a decrease in risk associated with LDL-c lowering (statins). Traditional drugs like nicotinic acid, fibrates like gemfibrozil, fen fibrate, and Pema- fibrate, and omega-3 fatty acids like docosahexaenoic acid and eicosapentaenoic acid are all feasible alternatives. The first step in treating diabetic dyslipidemia should be a change in lifestyle, including the creation of a healthy diet, the implementation of a regular exercise routine, and the management of the typical anxiety experienced by many patients. It goes without saying that proper blood glucose control should exist before lipid medication is started.

Keywords*: covid, diabetes, Apolipoprotein B*

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INTRODUCTION:

Patients diagnosed with Pandemic Coronavirus (COVID-19) may experience a worsening of their condition when comorbidities are present [1-3]. One of the most significant risk factors for COVID-19 was diabetes, according to papers based on a meta-analysis that proved this [4], closely followed by hypertension. Persons with diabetes mellitus (DM) are not more likely to get coronavirus, but they are more likely to have problems as a consequence of the infection. It is not a lack of insulin synthesis that is connected to decreased immunity; rather, it is increased blood sugar. People with diabetes who have a very high body mass index are more likely to have higher levels of inflammation, which may have an adverse influence on immunity. Blood sugar management may reduce COVID-19 risk to levels equivalent to those of those without diabetes. No matter what kind of diabetes a person has, their risk of complications rises if they are over 60, have linked prior conditions (such as high blood pressure), or have both. Insulin resistance without diabetes poses no difficulties. There is currently no known treatment or prevention for COVID-19 that utilizes any vitamin, serum, alternative medicine, or therapy that is believed to enhance immunity. It is not possible, based on the data that is now available and the degree of evidence that is present, to say that pre diabetic people are at a higher risk of contracting a coronavirus infection. It is important to determine whether or not individuals in their senior years or those who have other related disorders have prediabetes. Any patients, regardless of whether or not they are at risk, should adhere to the same basic recommendations to limit the disease's spread, as well as all recommendations made by the most recent health authorities. Patients who are currently using Captopril, Enalapril, Losartan, Aspirin, or Pioglitazone should continue taking their medications as directed by their physicians since there is no evidence to suggest that these medications should be discontinued.

To emphasize, in this study we demonstrate two of them, as well as their interaction, which might function in a way that contributes to the worst possible result of COVID-19. Diabetes and hyperlipidemia are two variables that have the potential to interact with one another in this function. As an independent risk factor, diabetes mellitus (DM) is considered to be high. The leading cause of mortality in this patient population is atherosclerosis. Two times the chance of developing coronary disease, three times the risk of developing a stroke, and four times the risk of developing symptomatic peripheral vascular insufficiency are all associated with this condition [5]. We show you two of them here, along with how they interact with one another, both of which may contribute in an additive manner to the worst possible COVID-19 conclusion. Diabetes and hyperlipidemia are two variables that have the potential to interact with one another in this function. Diabetes mellitus (DM) is an increasing risk factor for coronary artery disease. Atherosclerosis is their major cause of death. Coronary disease risk doubles, stroke risk triples, and peripheral vascular insufficiency symptomatic risk quadruple [5].

In people of all ages, having diabetes raises their risk for cardiovascular disease. Although the risk of atherosclerotic disease is higher in men, it is higher in women with diabetes, especially at younger ages [6]. This heightened danger is similar to that seen in men. Several things contribute to the increased risk of atherogenesis in people with diabetes and atherosclerotic disease. The most significant of these risk factors are obesity, hypertension, fibrinogen levels, and dyslipidemias, all of which often occur together [7,8].

Dyslipidemias are secondary to diseases and metabolic alterations: Type 2 diabetes and metabolic syndrome may be related. In this group, heart disease is the main cause of death, and all of these risks are linked to insulin resistance. Quantitative, qualitative, and kinetic anomalies characterize the components of dyslipidemia in DM2. In the lab, you could see a wide range of phenotypes, such as a) Postprandial lipemia characterized by an increase in chylomicrons and a decrease in HDL-c; b) Mixed dyslipidemia has high plasma triglycerides.

Pathophysiology: Significant factors in the etiology of type 2 diabetes and dyslipidemia include insulin resistance and visceral obesity [15]. Hypertriglyceridemia is made worse by low lipoprotein lipase activity, which may be caused by insulin resistance or an insufficient supply of insulin [16]. Increased cholesterol ester carrier enzyme activity in diabetes partially explains lipid and atherogenic abnormalities in type 1 and type 2 diabetes. Cholesterol esters are shuttled from other lipoproteins, most notably HDL, to VLDL at the discretion of the cholesterol ester carrier enzyme, which is more active under these circumstances (VLDL). Also, very low-density lipoproteins (VLDL) are responsible for transferring triglycerides to HDL and LDL, both of which may be deficient in cholesterol esters [17,18]. Triglyceride-rich HDLs and low-density lipoproteins (LDLs) with low amounts of cholesterol ester are converted by lipoprotein lipase and hepatic lipase into smaller, denser particles that are more prone to induce atherosclerosis. Although they contain fewer cholesterol esters, small and dense LDL particles are relatively frequent. This leads to a

lipid profile where LDL-c values are normal or low, but apo B levels are quite high, which may mask the atherogenic potential [19-21]. Diabetic dyslipidemia is exacerbated by a number of factors, including hereditary forms of dyslipidemia, obesity, inactivity, hyperglycemia management, and the presence of comorbidities such as nephropathy.

Lipid changes in diabetic patients: An uncontrolled condition or the use of medicines (diuretics, beta-blockers), etc, for comorbidities, may both contribute to dyslipidemias in diabetic patients. Both of these possibilities are possible in diabetic patients. They are nonetheless capable of playing a key role while being connected to the genetic component. Hypertriglyceridemia, which is often accompanied by hypoalphalipoproteinemia [9], is the kind of blood lipid abnormality that occurs most frequently in diabetes patients whose condition is not well managed. Reduced insulin levels, which encourage less lipoprotein lipase activity, are seen in patients with insulin-dependent diabetes whose disease is poorly controlled. Triglyceride hydrolysis by this enzyme lowers chylomicron and very low-density lipoprotein metabolism by releasing free fatty acids and glycerol (VLDL). Additionally, lipolysis in adipose tissue is increased with insulin deficiency, leading to a greater release of free fatty acids [10]. Hepatocytes utilize free fatty acids to make VLDL (VLDL). There is evidence that insulin resistance in non-insulin-dependent diabetics leads to an increase in the non-insulin-dependent liver, which in turn leads to hypertriglyceridemia. When the liver is fed a lot of glucose and free fatty acids, it cranks out more very low-density lipoprotein (VLDL) [10]. Additional research low-density that non-insulin-dependent diabetic patients have higher concentrations of very low-density lipoproteins (VLDL) in the postprandial period [11]. This was seen in a study comparing individuals with non-insulin-dependent diabetes to healthy controls with normal glucose tolerance. Several institutions are studying the function of postprandial VLDL in atherogenesis. Several studies [12] link this to atherosclerosis. Insulin-dependent diabetics with poor control have a decreased supply of HDL-c components. Lipoprotein lipase metabolizes chylomicrons and VLDL to create these molecules, but its activity diminishes as insulinemia falls [9,10].

Hypo-alphalipoproteinemia has been connected to improved action of the hepatic lipase enzyme [9,10], which catalyzes HDL-c. Higher levels of insulin resistance are believed to be responsible for this enzyme's enhanced activity. Evidence suggests HDL-c is excreted selectively in the urine, further decreasing blood levels [10]. Diabetics with renal impairment seem to be at greater risk for this condition. As far as the LDL-c (low below-densityrotein cholesterol) component goes, Diabetics seem to have more qualitative than quantitative changes. According to the findings of the NHANES II research, the group of diabetes patients has LDL-c values that are significantly greater than those seen in the general population. Nevertheless, the results of previous studies including people who have this condition [13] have shown that this modification is not always present.

Even among diabetic patients who have normal lipid levels, there is a significant incidence of smaller and denser LDL-c particles. [14] This is true even when diabetic persons have normal lipid levels. The severity of non-enzymatic glycosylation as well as lipid peroxidation increases in diabetics whose disease is not well managed, leading to the development of lipoproteins that are glycosylated and oxidized, and hence have a larger atherogenic potential.

Treatment: Unregulated blood sugar, an inadequate diet, a lack of physical activity, obesity, and excessive alcohol use all contribute to the worsening of diabetic dyslipidemia, which makes therapy all the more important. Weight reduction, dietary changes, and aerobic activity are examples of lifestyle changes that fall within the purview of the first therapy line for diabetes and dyslipidemia.

Laboratory evaluation of lipid profile in DM 2: Although cholesterol levels may be normal, a laboratory evaluation of the lipid profile in type 2 diabetes reveals the presence of an atherogenic lipid profile. This atherogenic lipid profile is caused by an increase in the levels of all three lipoprotein classes (LDLs, HDLs, and IDLs) [22, 24]. No matter how much cholesterol or how densely packed an LDL particle is, there is always one apo B molecule within. Normal LDL-c levels together with increased apo B [25] indicate the presence of many small, dense LDL particles in circulation. Consequently, apo B levels in the serum are more indicative of cardiovascular risk than LDL-c levels in the plasma [26]. In the Diabetes Management and Complications Trial (DCCT), intensive care was not related with changes in LDL-c or HDL-c levels, but it was linked to lower levels of apo B and Lp (a). Therefore, it is essential to evaluate non-conventional laboratory risk factors in diabetes patients, as was highlighted here [27].

Non-HDL cholesterol is another method that may be used to analyse lipoproteins high in triglycerides, and this method does not need the administration of apo B. It is simple to use, has a low associated cost, and may be used to the segment as well as the assessment of lipid-lowering medication in these individuals. It is generally agreed that non-HDL cholesterol is the most

accurate predictor of the risk of cardiovascular disease in this group [28].

Effects of hypoglycemic drugs on lipoproteins: The influence of hypoglycemic medications on lipoproteins include the following: dyslipidemia in type 2 diabetes may be partially rectified by insulin therapy and glycemic management, which results in a decrease of triglycerides and an increase of HDL-c [29,30]. Metformin, which is extensively used in the treatment of diabetes and lowers insulin resistance, also lowers hypertriglyceridemia, despite the fact that it is solely regarded to be hypoglycemic [29,31]. This is because metformin is an insulin sensitizer. Other diabetic drugs may have either a beneficial or harmful impact on lipoproteins, depending on the individual patient (Table 1). The recent considerable reduction in the frequency of cardiovascular events found with empagliflozin is unlikely to be attributable to the influence that the medicine has on a person's lipid profile, as seen by the little rise in LDL-c shown with sodium-glucose cotransporter inhibitors 2 (SGLT2) [32].

Table 1: Lipid-lowering drugs' effects on HDL and LDL levels.

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

(↑ = Increase), (↓ = Decrease), (↔= No Change)

Lipid-lowering: Lipid-lowering: The level of LDL-c causes the development of cardiovascular disease for which there is the most evidence. When compared with non-diabetic patients, diabetic patients have higher death ratios from cardiovascular disease [51]. This risk can change depending on the cholesterol levels in the diabetic patient's blood. As a result, LDL-c is an important therapeutic target for lowering the risk of cardiovascular disease.

HMGCoAredutase Inhibitors: Statins, which are HMGCoAredutase inhibitors, are the medications of choice for treating dyslipidemia in diabetic individuals. Inhibiting Hydroxymethylglutaric acid coenzyme A reductase has the main impact of lowering plasma levels of LDL-c by reducing the role of the enzyme that plays a limiting role in cholesterol production. In addition to reducing plasma levels of lipids, it also enhances the expression of LDL-c receptors in the liver and the rate at which LDL-c is eliminated from the body. When it comes to reducing the risk of cardiovascular disease-related death and disability among both diabetics and the general population, statins are the gold standard [52,53]. LDL-c levels are not significantly increased in diabetic dyslipidemia, however, this is nonetheless the case. It seems that statins have the same potential for relative risk reduction in those with and without diabetes. On the other hand, diabetics have a lower NNT to treat and avoid an incidence as compared to non-diabetics [54]. The dosage of statins taken is directly proportional to the amount of risk that is reduced; larger doses result in greater risk reductions. Even when treated with statins, diabetics still have a risk of experiencing a cardiovascular incident one time every seven years. However, it is possible that the populations investigated were not typical of younger people or patients with severe renal disease. The use of statins for both primary and secondary diabetes prevention is

supported by strong evidence from clinical research. Research on these subgroups is necessary, and good clinical judgment is essential when prescribing medication.

Fibrates and nicotinic acid: In addition to fibrates and nicotinic acid, high triglycerides, low HDL-c, and non-HDL-high cholesterol raise residual risk in this group. Fibrates, which reduce plasma triglycerides by 30–50%, are being studied as adjuvants in the treatment of chronic hypertriglyceridemias. The risk of pancreatitis may be decreased by starting therapy as soon as feasible when fasting triglycerides are more than 500 mg/dL [61,62]. By activating PPAR-(peroxisome proliferator-activated receptor-) agonists, they suppress lipid, inflammatory, and atherogenic changes [63]. Enhancing intravascular lipolysis and decreasing levels of apolipoprotein C-III (apo C-III) and apolipoprotein A-V may be achieved by taking these drugs since they increase lipoprotein lipase activity (apo A-V). They increase the synthesis of HDL-c, apolipoproteins A-I and A-II, the SREBP1 receptor, and the ABCA1 transporter [63], which in turn increases the rate at which reverse cholesterol transfer occurs.

Combining fibrates and statins raises the risk of muscular injury. However, correlations between some fibrates such as gemfibrozil and statins are illegal [64, 65, 66]. In the VA HIT trial, secondary prevention patients received gemfibrozil instead of a placebo. The researchers found that this led to a 24% decrease in the number of combined events. When the idea for this research was created, statins were not commercially accessible [67, 68, 69, 70].

Inhibitors of the absorption of cholesterol in the digestive tract: Ezetimibe inhibits cholesterol absorption. It prevents cholesterol from entering small intestine enterocytes [55]. This reduces plasma cholesterol by 15% to 20% without compromising fat-soluble vitamin absorption [56]. By attaching to Niemann-Pick C1-Like 1 in intestinal brush-edge cells, ezetimibe lowers cholesterol absorption. In the IMPROVE-IT Study, 18,144 ACS patients were assessed. 27% had diabetes. During a 6-year follow-up, the group given simvastatin 40 mg plus ezetimibe 10 mg experienced fewer combined events than the simvastatin-only group. This research showed additional advantages in decreasing LDL-c, validating the concept that lower LDL-c objectives should be attained to minimise residual risk [58]. In addition, non-statin medicines showed further advantages. Cholestyramine may reduce LDL-c levels, however it raises triglycerides and is not well tolerated [59]. Cholesevelam lowers glycated haemoglobin (Hb A1c), total cholesterol, and LDL-c by 20% [60].

Omega-3 fatty acids: Two marine-derived omega-3 fatty acids, DHA and EPA, have positive effects on the cardiovascular system, making omega-3-rich fish an important element of a balanced diet. In spite of the benefits, there is insufficient evidence to confidently recommend taking fish oil capsules as a dietary supplement for the purpose of preventing cardiovascular disease. Taking an EPA/DHA supplement of 2–4 grammes per day has been shown in studies [72,73] to reduce triglyceride levels by 25–30%, increase HDL-c by 1-3 percentage points, and decrease LDL-c by 5–10 percentage points. Anti-inflammatory and antiarrhythmic, improved endothelial function, effects that reduce the risk of sudden death, and outcomes for cardiovascular health. The effect of EPA and DHA supplementation on mortality from cardiovascular disease was either insignificant or nonexistent in the studies (evidence of moderate quality). There is some evidence, albeit of a low quality, to suggest that taking the supplement reduces the risk of cardiovascular events such as cardiovascular mortality and arrhythmia [74].

New drugs: Anti-PCSK9 antibodies are the most recent and major advance in cholesterol-lowering medication. They lower LDL-c to levels that have never been seen before, particularly when combined with statins and/or ezetimibe as treatment.

The liver is the primary organ responsible for the synthesis of the PCSK9 protein; the colon, brain, and pancreas all contribute, but to a lesser extent. As a result of its ability to control the expression of low density lipoprotein receptors in the liver, it plays a decisive part in the determination of plasma LDL-c concentrations (LDLR). Hepatocyte-secreted PCSK9 targets the liver's LDLR receptor. After being taken in, its contents are degraded in lysosomes along with the receptor complex and lipoprotein. To put it another way, this blocks the LDLR from returning to the liver's outer layer. The decline in the number of these receptors causes a reduction in the clearance of LDL particles, boosting the concentration of this lipoprotein in the blood [75, 76, 77].

Pharmacological treatment: sufficient blood glucose control should be accomplished before beginning lipid medication. This is a prerequisite for the treatment. Diabetes mellitus patients who are treated with insulin or with oral hypoglycemic agents may also see a favorable change in their lipid profile. Insulin normalises lipoprotein lipase activity, improving VLDL catabolism and HDL synthesis (HDL-c). Metformin, a biguanide, improves lipid profiles while reducing glycemia and VLDL in hypoglycemic individuals. Validated.

As long as non-pharmacological approaches, proper blood glucose management, and other putative

secondary causes of dyslipidemia fail to normalise serum lipids, the introduction of hypolipidemic medications is warranted [85]. This is true even if other putative secondary causes of dyslipidemia have been eliminated. The vastatins are the first line of treatment for people with isolated elevations in LDL-c. Fibrates are the first line of treatment for both isolated cases of hypertriglyceridemia and mixed dyslipidemias. Due to the possibility of an increase in triglyceride levels and nicotinic acid as a consequence of an rise in insulin resistance, it is suggested that bile acid sequestering resins not be employed [86].

Non-pharmacological treatment: The first line of defence against dyslipidemia in a diabetic should be a change in lifestyle, including the creation of a healthy diet, the implementation of regular exercise, and the management of the typical anxiety experienced by many diabetics. Treatment that doesn't include drugs is behavioural modification, which includes things like figuring out how to eat well, getting more exercise, and calming the worry that plagues so many people. The patient's preferences and the patient's socioeconomic circumstances should be taken into consideration when formulating the diet plan. Combating obesity should be a priority. The total number of calories consumed need to be enough for the purpose of achieving or maintaining the ideal level of body weight.

The appropriate distribution of carbohydrates and fats within the diet makes it easier to achieve more favorable results in terms of blood glucose and lipid profile. Complex carbs, which should make up between 50 and 55 percent of one's daily caloric intake, should be substituted for simple carbohydrates. The overall proportion of fats should not be more than thirty percent, and the amount of saturated fat should be lower than ten percent. The recommended maximum daily consumption of cholesterol is 300 milligrams. Greater constraints may be imposed on the situation depending on the requirements of each individual instance [80,81]. It is essential to encourage the consumption of soluble fibers at a rate of 35 to 40 grams per day because their consumption reduces levels of postprandial prandial powders, serum cholesterol, and glycemia [82]. This is why it is important to encourage the consumption of soluble fibers at this level. Abuse of alcohol must be avoided for a number of reasons, one of which is the chance that it will raise triglyceride levels. Another reason is that it will create more favorable circumstances for liver dysfunction. Glycemic management is made easier by the increase in glucose uptake that results from consistent physical activity as well as the reduction in insulin resistance that this produces. Increases HDL-c levels while simultaneously lowering triglyceride levels, resulting in an improved lipid profile [83,84].

Conclusion: Assembling medications may be necessary if target lipid levels are not achieved. The addition of a vastatin to the treatment of hypertriglyceridemia in patients may be helpful, especially when the condition persists after the use of a full dosage of medicine from the fibrate group. Rare instances of hepatitis and rhabdomyolysis due to this medication regimen may be detected with anamnesis and periodic assessment of transaminases and creatine phosphokinase. Although it seems sensible to employ antioxidants since they prevent the oxidized form of lipoproteins from forming, long-term studies haven't proven this technique yet. . Finally, individuals with dyslipidemia due to diabetes should undergo vigorous treatment aimed at reversing the metabolic abnormalities detected in accordance with their individual cardiovascular risk via a combination of lifestyle changes and medication. By achieving this milestone, patients will be better able to mount an immune response to an infection, such as the dangerous COVID19 pandemic.

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