International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Diabetic Dyslipidaemia: The Association between Diabetes Mellitus and Deviations of Lipid Metabolism

Nesrin Shiekh Sulyman[1], Fatima Ibrahim Mohamed Abdulla[2]

[1]Internal medicine consultant, Primary Health Care Corporation, Qatar

[2]Family Medicine Specialist Physician, Primary Health Care Corporation, Qatar

Abstract: ***One of the most serious macrovascular consequences of diabetes mellitus is diabetic dyslipidaemia. Diabetic dyslipidaemia has a prevalence and incidence that is similar to diabetes mellitus. Aim of the current study was to investigate the association between diabetes mellitus and deviations of lipid metabolism, the study also explored the numerous challenges that treat diabetic dyslipidaemia. Methodology: The current study was searched using a variety of key words such as "Diabetes mellitus and/or Dyslipidaemia" "Dyslipidaemia and/or Insulin resistance", "Dyslipidaemia and/or Type 2 diabetes" and "Type 2 diabetes and/or complications", "Dyslipidaemia and/or complications", "Diabetic dyslipidaemia and/or obesity", "Obesity and/or complications", "Diabetes mellitus and/or Hyperlipoproteinemia". Those articles were derived from the data related to diabetes mellitus and/or dyslipidaemia and reported cases were conducted utilizing seven electronic databases (CINAHL, MEDLINE, ProQuest, PubMed, Scopus, Science Direct, and Cochrane) for studies published in various languages from January 2021 to May 2021. According to the findings, diabetic dyslipidaemia is a common illness in which insulin resistance is thought to be the main force behind the lipid abnormalities. Hypertriglyceridemia, low HDL cholesterol, and high small dense LDL levels are all related physiologically, with hypertriglyceridemia being the most prominent trait. Diabetic dyslipidaemia can be effectively managed to reduce the risk of CVD. The most essential treatment techniques are lifestyle and pharmaceutical therapies. The most effective way to reduce cardiovascular risk in diabetes patients is to take statins on a regular basis. In the search for new therapeutic strategies, it's critical to improve our understanding of the pathophysiology of lipid abnormalities in diabetic patients and to expand our knowledge of existing lipid-lowering drugs so that their role in the management of diabetic dyslipidaemia can be clearly defined. The study emphasizes the detrimental consequences of dyslipidaemia.***

Keywords: Dyslipidaemia; Insulin resistance; Type 2 diabetes; Diabetic dyslipidaemia; Hyperlipoproteinemia type II.

1. Introduction

1.1 Background

Diabetes is a disease of hyperglycaemia caused by a lack of insulin action, but insulin also has a significant impact on serum lipids. Dyslipidaemia (abnormal lipid levels in the blood) is frequent among diabetics, regardless of whether they have insulin insufficiency or insulin resistance. Low-density lipoprotein (LDL)-cholesterol (C) is without a doubt the most significant risk factor for atherosclerotic cardiovascular disease (CVD), such as coronary artery disease. In diabetics, however, severe hypercholesterolemia is uncommon; instead, hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) are more common (Hirano, 2018). Diabetic dyslipidaemia (DD) is a key characteristic of diabetes mellitus (DM) that is closely and causally associated to its macrovascular consequences **(Vijayaraghavan, 2010)**. The number of individuals with diabetes, particularly type 2 diabetes mellitus (T2DM), has risen to 350 million worldwide in the recent few decades **(Taskinen and Borén, 2015),** and it is expected to climb to 592 million by 2035 **(Zimmet, et al, 2014; Taskinen and Borén, 2015).** The number of adults with diabetes is expected to rise by 20% in industrialized countries and 70% in developing countries during the next 20 years **(Whiting, et al., 2011)**.

The global incidence of diabetes has risen at an unprecedented rate in recent decades, with estimates predicting that the number of individuals with type 2 diabetes would rise from 350 million now to 592 million by 2035. **(Guariguata, et al., 2014; Zimmet, et al., 2014).** Between 2010 and 2030, the number of adults with diabetes in affluent countries is anticipated to rise by 20%, whereas it will rise by 69 percent in underdeveloped countries **(Whiting, et al., 2011; Shaw, et al., 2010).** Diabetes is becoming more prevalent around the world, posing a significant illness burden on both the population and individuals, as well as the health-care system as a whole. Despite recent considerable breakthroughs in therapeutic techniques to reduce CVD risk factors, CVD remains the leading cause of morbidity and mortality for people with T2DM **(Joseph, and Golden, 2014).** Diabetes is expected to decrease the life of a 50-year-old individual by six years on average, with increased vascular disease accounting for around 58 percent of this effect **(Seshasai, et al., 2011).** Although the gap in CVD risk between people with and without diabetes has reduced significantly in recent decades, there are still strong links between diabetes and vascular outcomes **(Gregg, et al., 2014; Faerch, et al., 2014; Sarwar, et al., 2010).**
According to recent studies, diabetes raises CVD risk by around twofold on average, however the risk varies greatly depending on the demographic **(Sattar, 2013).** Those with diabetes and coronary heart disease, in particular, are at a much-increased risk of future CVD events **(Taskinen, et al., 2015).**

If well-controlled with insulin, type 1 diabetes mellitus (T1DM) is linked with few, if any, lipid metabolic problems. In a group of young T1DM patients, high LDL-C and high

triglyceride-rich lipoproteins (TGLs) were discovered in 15.8% and 12.9 percent, respectively. DD manifests in a form similar to that connected to T2DM only in individuals with poorly controlled T1DM and those at risk of developing obesity or metabolic syndrome (MetS) **(Bulut, et al., 2017).** Hyperinsulinemia, insulin resistance, and cell failure are all associated with DD in T2DM patients; plasma levels of fasting TRLs, small-dense LDL-C particles, and low levels of HDL-C are all raised **(Athyros, et al., 2018)**.

Both glucose and lipids are crucial components of energy metabolism. It's hardly surprising, then, that glucose metabolism and lipid metabolism are inextricably intertwined. This has a lot of ramifications in terms of medicine. As a result, diabetic people have a typical dyslipidaemia, which is intimately associated to cardiovascular disease. Hypertriglyceridemia and low HDL-C, on the other hand, might cause glucose metabolism problems and hence be the cause and source of hyperglycaemia. Surprisingly, statin therapy is linked to a tiny but considerable increase in the rate of new onset diabetes, but in almost all clinical scenarios, the benefit of statin therapy surpasses the risk. Lastly, patients with familial hypercholesterolemia have a lower risk of developing T2DM, however this is dependent on the severity of the LDL increase (the higher the LDL-C the lower the risk). Understanding the underlying biology is critical for better addressing clinical concerns and developing innovative anti-dyslipidaemia and anti-diabetes therapies **(Parhofer, 2015).**

Overproduction and increased clearance are to blame for higher TRLs. The main qualitative lipoprotein abnormalities are an increase in big VLDL1 and small-dense LDL-C particles, both of which are sensitive to oxidation, as well as increased TG content in both LDL-C and HDL particles and apolipoprotein glycation. Increased VLDL1 synthesis, decreased VLDL catabolism, and increased HDL catabolism are all kinetic anomalies of lipoproteins in T2DM and DD **(Wang, et al., 2012).** All of the above, which have been shown to be inextricably related, are key risk factors for the development and progression of atherosclerosis. **(Arca, et al., 2012)**. Though LDL-C levels are normally normal in most cases of DM, their particles have a slower turnover, which is potentially atherogenic. Insulin resistance (IR), which affects the activity of lipoprotein lipase (LPL), cholesterol ester transfer protein (CETP), phospholipid transfer protein (PTP), endothelial lipase (EL), and hepatic lipase, is usually associated with such lipoprotein abnormalities (HL). IR, visceral obesity, and non-alcoholic fatty liver disease are all linked to DD (NAFLD) **(Athyros, et al., 2017)**.

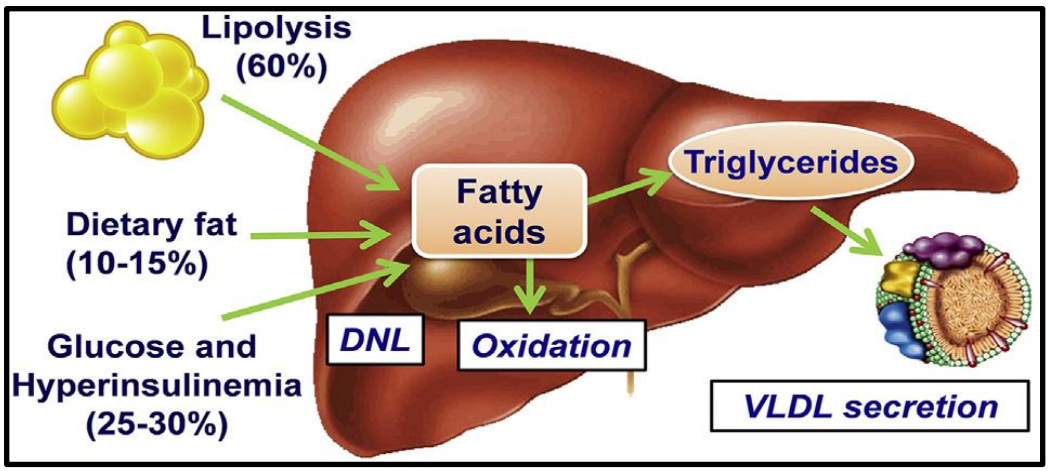

Figure 1: The role of numerous metabolic pathways in human liver steatosis. In hepatic triglyceride deposition, fatty acid oxidation and triglyceride export seem to play modest roles. In steatotic livers, however, increased availability of fatty acids from adipose tissue through uninterrupted lipolysis and de novo lipogenesis (DNL) from glucose are the primary sources of lipids. Figure modified from Ferre P and Foutelle F **(Ferre and Foutelle, 2010; Taskinen and Borén, 2015).**

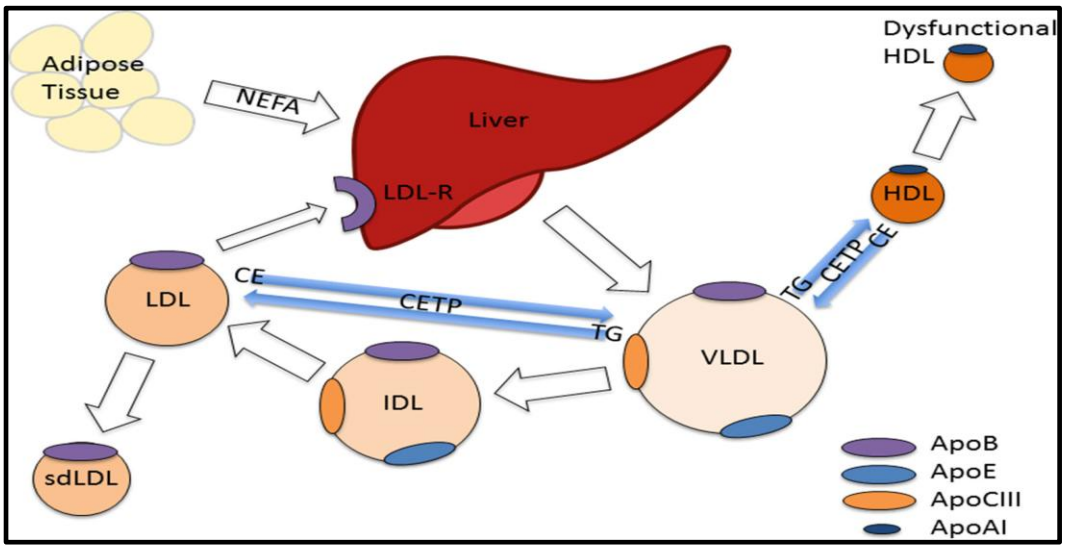

Figure 2: Qualitative changes in lipoproteins in diabetes **(Schofield, et al., 2016)**

Diabetic nephropathy (DN) and diabetic retinopathy are common complications of dyslipidaemia, which is a major risk factor for CVD (DR). Dyslipidaemia management in DN patients is critical because individuals with DN have a high risk of CVD-related death. Dyslipidaemia has also been found to have an important role in the development and progression of DN **(Rutledge, et al., 2010; Hammer and Busik, 2017; Zhou, et al., 2018).** Patients with diabetes have abnormal lipoprotein metabolism, as evidenced by increases in VLDL-C and LDL-C and a decrease in HDL-C. **(Hirano, 2014).** Quality alterations, such as tiny dense LDL, are in addition to these quantitative changes. **(Chehade, 2013; Kawanami, et al., 2016).**

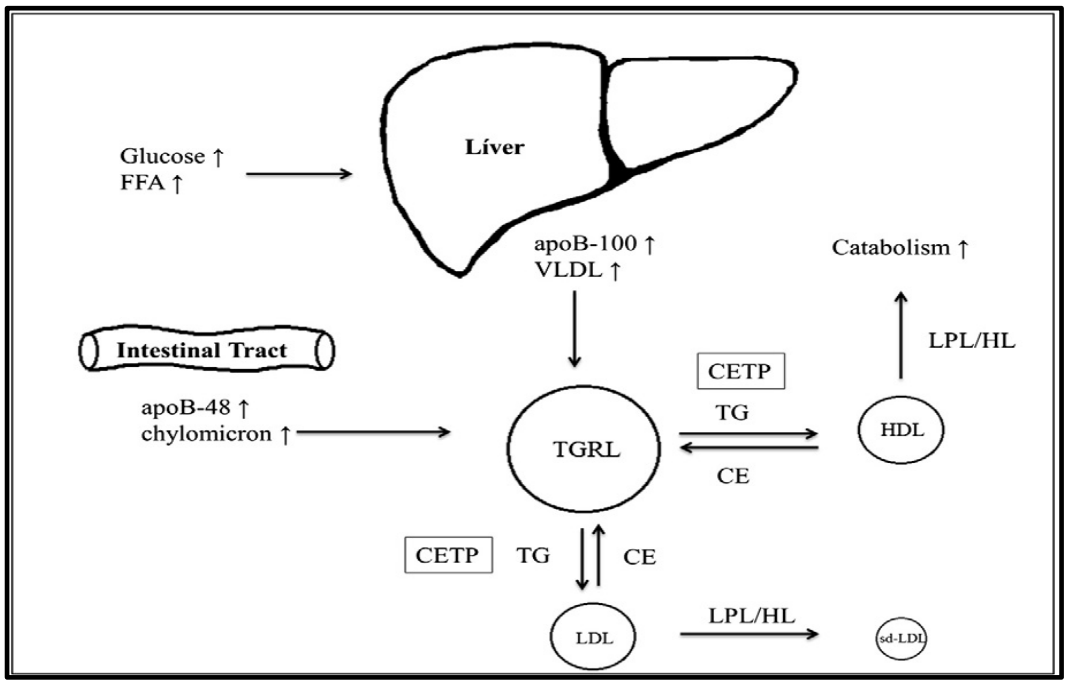

Figure 3: Effects of diabetes on TGLs, HDL and LDL. Increased availability of glucose and free fatty acids in the liver leads to decreased degradation of apoB-100 and increased secretion of VLDL. In the postprandial state, apolipoprotein B (apoB)-48 and chylomicrons are produced at a higher rate in the intestinal tract. Both liver-derived VLDL and intestinal-derived chylomicrons contribute to the overabundance of TGLs in blood. CETP facilitates the exchange of TG and CE between TGLs and LDL as well as HDL. Subsequently, triglyceride-rich LDL and HDL are hydrolysed by LPL or HL. apoB, CETP, free fatty acids (FFA); HDL; HL; LDL; LPL; small-dense low-density lipoprotein (sd-LDL), TG; TGRL **(Wu and Parhofer, 2014).**

Insulin resistance is linked to an increase in fatty acid flow to the liver, which leads to an increase in VLDL synthesis. Insulin fails to decrease lipolysis and FoxO1 (a transcription factor that regulates gluconeogenesis and glycogenolysis via insulin signalling and also adversely regulates adipogenesis), but it can still activate the rapamycin complex 1. (mTORC1). Increased expression of microsomal triglyceride transfer protein (MTTP) and apoCIII results from the effect on FoxO1, which promotes VLDL overproduction and reduces clearance. Insulin also inhibits apoB48 production

and chylomicron secretion **(Abumrad and Davidson, 2012),** whereas insulin resistance leads to chronic intestinal overproduction of apoB48, which contributes significantly to both NAFLD and postprandial lipemia, both of which are emerging and important CVD risk factors. **(Davis, et al., 2013; Schofield, et al., 2016).**

In T2DM patients, the link between DD and CVD dyslipidaemia raises the risk of CVD. Although hypertriglyceridemia, low HDL, and increased small dense LDL concentrations have all been linked to CVD, the relative contribution of each to the development of atherosclerotic vascular disease is still unknown. Although there is a well-established link between LDL and atherosclerosis, there isn't one for HDL **(Shah, et al., 2013).** TGLs may possibly play a causative role in CV events, according to newer evidence. **(Blood, et al., 2014; Jorgensen, et al., 2014; Do, et al., 2013)**. When compared to non-diabetic persons, T2DM sufferers may not have a greater LDL concentration. However, there is a significant increase in small dense LDL particles, implying that diabetes patients have a greater number of LDL particles at a given LDL cholesterol content. Small dense LDL particles are more atherogenic than large buoyant LDL particles because they are more likely to be eliminated by scavenger receptors, which is an early essential step in atherosclerosis. Even when LDL levels are below the National Cholesterol Education Program target of 130 mg/dl, LDL cholesterol remains a powerful independent predictor of CVD in diabetes people. In diabetic patients, every 10 mg/dl rise in LDL-cholesterol increased CVD risk by 12%, according to the Strong Heart Study (**Wu and Parhofer, 2014).**

In people with T2DM, cardiovascular disease is a leading cause of death. Dyslipidaemia is common in children with T2DM and is a known risk factor for cardiovascular disease (CVD). In this review, we look at the epidemiology, pathophysiology, and therapeutic recommendations for dyslipidaemia in children with T2DM. Dyslipidaemia is complex and linked to poor glycaemic management, insulin resistance, inflammation, and hereditary vulnerability, according to recent findings. Lipid screening is recommended after establishing glycaemic control and then once a year thereafter, according to current standards. LDL-C 100 mg/dL, HDL-C > 35 mg/dL, and TG 150 mg/dL are the lipid targets. Summary After 6 months, if LDL-C remains above 130 mg/dL, With a treatment objective of less than 100 mg/dL, statins are suggested. Fibrates are suggested if fasting TG is > 400 mg/dL or non-fasting TG is > 1000 mg/dL. Despite the fact that aberrant levels of atherogenic TG-rich lipoproteins, apolipoprotein B, and non-HDL-C are frequent in paediatric T2DM, they are not routinely measured in risk assessment or intervention **(Sunil and Ashraf, 2020).**

In many respects, glucose and lipid metabolism are intertwined. Diabetic dyslipidaemia, defined by increased triglycerides, low HDL-C, and a predominance of small-dense LDL particles, is the most common clinical manifestation of this interaction. However, we have learnt in the last decade that the interplay is far more complicated. Hypertriglyceridemia and low HDL-C can be both the result and the cause of a malfunctioning glucose metabolism. Furthermore, statins are now widely known to be linked to a minor but considerable increase in the chance of developing new onset diabetes. The fundamental mechanisms are unknown, however modification of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA)-reductase may play a key role, as genetic data show that mutations that cause decreased HMG CoA-reductase activity are linked to obesity, higher glucose levels, and diabetes. This statin-induced increased risk for new onset T2DM is not detected in people with familial hypercholesterolemia, which is quite fascinating. In addition, patients with familial hypercholesterolemia appear to have a decreased risk of T2DM, which appears to be dose-dependent (the higher the LDL-C, the lower the risk). Whether or whether there is a link between lipoprotein(a) and diabetes is still up for dispute **(Parhofer, 2015).**

All patients over the age of 40 should take statins, according to the 2017 American Diabetes Association (ADA) guidelines for diabetes care. A high-intensity statin is suggested for people aged 45 to 70 who have CV risk factors or illness. Patients in this age range who have had an acute coronary syndrome and have an LDL-C of 50 mg/dl or above, as well as those who have had a CVD event and are unable to tolerate high-dose statins, should get double hypolipidemic therapy with a moderate-intensity statin and ezetimibe. Patients over 75 years old who match the above-mentioned requirements should follow the same suggestions. Statin medication is linked to a modest increase in type 2 diabetes new onset. The pathology that underpins this condition is unknown. Reduced insulin sensitivity and altered -cell function can be caused by a variety of factors. This may trigger the onset of type 2 diabetes in predisposed individuals. 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) **(Jellinger, et al., 2017)**.

In diabetics, IR is the major mechanism that causes lipid abnormalities. Increased hepatic uptake of free fatty acids leads to greater triglyceride production. Peripheral resistance to insulin increases the release of free fatty acids from adipose tissue, which are taken up by the liver. Triglyceride synthesis is followed by increased ApoB secretion and hepatic formation of triglyceride-rich very low-density lipoprotein cholesterol (VLDL) **(Adiels, et al., 2005).** Through the action of the CETP, triglyceride-rich VLDL enriches LDL and HDL, making them more cholesterol-rich. Hepatic or LPL hydrolyses these triglyceride-rich LDL molecules, resulting in the formation of tiny dense LDL. As a result, lipid abnormalities linked with diabetes are broad, extending beyond LDL increase, making it difficult to rely on traditional methods for lowering CV risk. **(Warraich, et al., 2017)**.

Diabetic dyslipidaemia treatment strategy. To improve lipid levels, lifestyle changes and glycaemic control should be adopted. The majority of patients, however, will require statin medication. Fibrates or omega-3 fatty acids may be administered in patients with isolated hypertriglyceridemia (elevated triglycerides and LDL-cholesterol 70 mg/dl); the relevance of statins in such people is unknown. Combination therapy may be considered in high-risk patients, although they have not been established in outcome trials. Statins combined with ezetimibe (a cholesterol absorption inhibitor)

can lower LDL cholesterol considerably. Statins combined with fibrates or omega-3 fatty acids lower triglycerides, but statins combined with bile acid resins lower LDL-cholesterol but may raise triglycerides. LDL stands for low-density lipoprotein; 3FA stands for omega-3 fatty acids; BAS stands for bile acid sequestrant. **(Wu and Parhofer, 2014)**.

Diabetes affects 463 million individuals globally, ranging in age from 20 to 79. **(Saeedi, et al., 2019).** Hypertension and hyperlipidaemia, commonly known as hypercholesterolemia, are prevalent comorbidities in people with T2DM, and their prevalence is rising **(Iglay, et al., 2016; Song, et al., 2016).** Continuous blood glucose control **(Schwarz, et al., 2018),** blood pressure (BP) control **(Thomopoulos, et al., 2017),** and blood lipid profile control can all help to lessen the risk of diabetes-related complications **(Patel, et al., 2008).** Most persons with diabetes should have a glycated haemoglobin (HbA1c) of 7.0 percent, blood pressure of 140/90 mmHg (130/90 for patients with increased CV risk), and LDL-C of 100 mg/dL, according to current ADA guidelines **(American Diabetes Association, 2018).** Diabetes self-management education and support, described as an interactive and ongoing process aimed at improving the knowledge, skills, and capacities needed for successful self-management of diabetes therapies **(Beck, et al., 2017),** has been shown to be effective **(He, et al., 2017; Sherifali, et al., 2015).** Similarly, in terms of increased medication adherence and improved blood pressure control, hypertensive patients may benefit from a combination of self-monitoring plus education or counseling. **(Williams, et al., 2018).**

Telemedicine is defined by three characteristics: Firstly; the use of information and communication technologies, secondly, the coverage of a geographic distance, and thirdly the involvement of professionals who provide direct care to a patient or group of patients. Patients with chronic conditions are claimed to benefit from it because it improves chronic care management and self-management. However, there is no evidence-based guidance on which components of telemedicine are most helpful for specific patient populations in currently available guidelines for the care of patients with diabetes, hypertension, or dyslipidaemia **(Timpel, et al., 2020).**

1.2 Statement of the problem

Diabetes is a well-known independent risk factor for CVD. Diabetic patients have a 2 to 4 times higher risk of stroke and death from heart disease than non-diabetic people. The elevated CV risk in diabetic patients is not entirely due to hyperglycaemia. Dyslipidaemia, which is characterized by a spectrum of quantitative and qualitative alterations in lipids and lipoproteins, is a relatively prevalent metabolic disorder linked with diabetes. Hypertriglyceridemia, a decrease in HDL-C content, and a shift toward small dense LDL are all frequent lipid abnormalities in diabetic dyslipidaemia (Sone, et al., 2011; Hirano, 2018). Fortunately, dyslipidaemia has the potential to exacerbate COVID-19 mortality and severity. The link was stronger in patients who were older, male, and had hypertension **(Atmosudigdo, et al., 2021).**

Diabetic dyslipidaemia is quite common in T2DM patients (prevalence ranges from 72–85 percent). Because DD plays a crucial role in the genesis and progression of atherosclerosis, this syndrome is linked to a significantly increased risk of CVD in compared to people without DM. The lipid abnormalities associated with DD are not only quantitative, but also qualitative and kinetic in nature. Increased TGs [it has been convincingly proven that TRLs and their remnants are atherogenic] and lower HDL-C are the predominant quantitative lipoprotein abnormalities of DD. **(Doucet, etal., 2012; Athyros, et al., 2018)**. We describe the biology of diabetic dyslipidaemia and discuss the role of dyslipidaemia in the development of type 2 diabetes in this review. We also present an update on management techniques, with an emphasis on dietary treatments and different pharmaceutical options.

1.3 Research Question

- What is the association between diabetes mellitus and deviations of lipid metabolism?
- What are the numerous challenges that treat diabetic dyslipidaemia?

1.4 Study Objective

The main aim of this study was to investigate the association between diabetes mellitus and deviations of lipid metabolism, the study also explored the numerous challenges that treat diabetic dyslipidaemia.

2. Methodology

2.1 Research Design

The current study was designed as integrated literature review to stand on the association between diabetes mellitus and deviations of lipid metabolism, the study also explored the numerous challenges that treat diabetic dyslipidaemia.

2.2 Data collection

The current study was searched using a variety of key words such as “Diabetes mellitus and/or Dyslipidaemia” “Dyslipidaemia and/or Insulin resistance”, “Dyslipidaemia and/or Type 2 diabetes” and “Type 2 diabetes and/or complications”, “Dyslipidaemia and/or complications”, “Diabetic dyslipidaemia and/or obesity”, “Obesity and/or complications”, “Diabetes mellitus and/or Hyperlipoproteinemia”. Those articles were derived from the data related to diabetes mellitus and/or dyslipidaemia and reported cases were conducted utilizing seven electronic databases (CINAHL, MEDLINE, ProQuest, PubMed, Scopus, Science Direct, and Cochrane) for studies published in various languages from January 2021 to May 2021.

2.3 Study inclusion criteria

All studies about the association between diabetes mellitus and deviations of lipid metabolism. Also, the studies that explored the numerous challenges that treat diabetic dyslipidaemia.

3. Discussions

High fasting and postprandial triglycerides, low HDL cholesterol, elevated LDL cholesterol, and a predominance of tiny dense LDL particles define diabetic dyslipidaemia. These lipid alterations are the main link between diabetes and diabetic patients' increased CV risk. Only a portion of the underlying pathophysiology is recognized. Overproduction and impaired catabolism of triglyceride rich lipoproteins of intestinal and hepatic origin are caused by changes in insulin sensitive pathways, increased concentrations of free fatty acids, and low-grade inflammation. This is mostly responsible for the observed alterations in HDL and LDL. Although lifestyle changes and glycaemic control can improve lipid profiles, statin medication provides the most effect in terms of lowering CV risk. As a result, most diabetic individuals should take statins. Other lipid-lowering medicines, such as ezetimibe, fibrates, omega-3 fatty acids, niacin, and bile acid sequestrants, have predominantly poor outcome trials, therefore their role is less clearly defined. The pathophysiology of DD and its link to CVD are examined in this review. Approaches to management will also be examined **(Wu and Parhofer, 2014).**

Children and Adolescents with T2DM: Epidemiology and Lipid Trends T2DM prevalence in children has continued to rise in tandem with rising obesity rates, disproportionately affecting racial and ethnic minorities. T2DM is present in 5.5 percent of non-Hispanic Whites and 37.6 percent of non-Hispanic Blacks in the United States **(Jensen and Dabelea, 2018).** In the SEARCH for Diabetes in Youth Study, 283 children with T2DM were found to have high total cholesterol (TC) values of more than 200 mg/dL, with 33 percent having elevated TC levels of more than 200 mg/dL. In children over the age of ten years, the prevalence of LDL-C > 160 mg/dL was 9%, and the prevalence of TG > 400 mg/dL was also 9%. HDL-C values below 40 mg/dL were seen in 44 percent of older youth with T2DM. Interestingly, despite the fact that 24 percent of those with T2DM had LDL-C levels that would require pharmacologic intervention if they were persistent and unresponsive to diet and lifestyle changes, only a small percentage of those with T2DM were receiving lipid-lowering therapy, highlighting the need for increased awareness among treating providers **(Kershnar, et al., 2006).** The SEARCH study also found that the percentages of children with T2DM who had poor glycaemic control had high TC, LDL-C, and TG concentrations were 65 percent, 43 percent, and 40 percent, respectively, in the SEARCH trial. **(Petitti, et al., 2007).**

Dyslipidaemia is very common in T2DM children and adolescents. Obesity, IR, hypertension, and a sedentary lifestyle are all common risk factors in children who are at risk. Because T2DM is a significant independent CV risk factor, it is critical to diagnose and treat dyslipidaemia to avoid CV morbidity. In T2DM, elevated serum TG, decreased HDL-C, and, on rare occasions, elevated LDL-C levels are typical dyslipidaemia patterns **(Mazzone, et al., 2008).** Elevated VLDL-C, non-HDL-C, tiny, dense LDL-C, and apo B 100 concentrations are among the various non-conventional lipoprotein abnormalities that are less typically tested. **(Pelham, et al., 2019)**.

Dyslipidaemia in T2DM Pathophysiology Insulin regulates cholesterol homeostasis and lipid metabolism. Obesity, metabolic syndrome, and hyperglycaemia in children and adolescents with T2DM exacerbate the dysregulated lipid metabolism. The relevant lipid and lipoprotein abnormalities are discussed in this section. In children and adolescents with T2DM, dyslipidaemia is extremely frequent. There is clustering of many CV risk factors in the presence of T2DM in a metabolically unwell child with obesity, exacerbating the risk of morbidity and mortality in maturity. Non-HDL-C, apo B, small dense LDL-C, and triglyceride-rich lipoproteins are not included in current T2DM dyslipidaemia therapy guidelines. Studies are needed to better understand the appropriate risk assessment and best treatments for dyslipidaemia in children with T2DM **(Sunil and Ashraf, 2020).**

T2DM dyslipidaemia is characterized by high triglyceride levels and low HDL-C, alterations that occur many years before clinically significant hyperglycaemia. According to new research, low HDL cholesterol is a risk factor not only for CVD but also for the development of diabetes (Abbasi, et al., 2013). Even before diabetes is formally diagnosed, these alterations, as well as the existence of tiny dense LDL particles, are likely to lead to accelerated atherosclerosis. Insulin insufficiency or resistance, adipocytokines, and hyperglycaemia are all possible contributors to the changes in lipid metabolism seen in diabetic individuals. Many parts of the etiology and effects of diabetic dyslipidaemia are unknown, however the mechanism that causes hypertriglyceridemia is well established **(Verges, 2015).** Insulin shortage or resistance enhances the release of non-esterified fatty acids (NEFA) from triglycerides stored in the more metabolically active centrally distributed adipose tissue. Hepatic triglyceride production is increased when there are high levels of NEFA in the blood. Increased apoB secretion is linked to increased hepatic triglyceride production. **(Warraich, et al., 2015; Schofield, et al., 2016).**

Weight loss, dietary changes, and aerobic exercise are the first-line interventions in the management of diabetic dyslipidaemia. Obesity raises insulin resistance and is increased to higher triglycerides, LDL cholesterol, and lower HDL cholesterol levels. Weight loss has been linked to changes in lipids and other cardiovascular risk factors, including the incidence of type 2 diabetes, and should be encouraged in obese diabetic patients. Caloric restriction remains the key to long-term weight management, and even small amounts of weight loss are linked to improvements in glycaemic control, HbA1c, and lipid profile **(Rock, et al., 2014).** Increased physical activity may be a useful supplement to food restriction, but it is unlikely to be effective on its own. Reduced fat consumption, especially saturated fat consumption, should also be recommended. The American Diabetes Association recommends a low-fat, low-saturated-fat, and low-cholesterol diet **(American Diabetes Association, 2014).**

Some saturated fat can be replaced with unrefined carbohydrate foods and some with oleic, linoleic, or omega-3 fish oils in individuals who do not have a significant increase in serum triglycerides but are not obese. Even with

long-term follow-up, dietary therapies, which are regarded first-line treatment for all diabetic patients, have not proven successful in demonstrating a mortality benefit **(Look, et al., 2014).** Orlistat, a gastrointestinal lipase inhibitor that causes fat malabsorption and should be given close to meals, induces fat malabsorption. Steatorrhea can occur if the patient does not follow a low-fat diet. There is frequently an initial benefit, but weight loss plateaus as the patient learns to skip it if they plan to have a fatty meal. Regardless, any weight loss can help to lower cardiovascular risk factors. Orlistat has a higher effect on serum total and LDL cholesterol levels than could be explained only by weight loss. Surgical weight loss is far more effective than medicinal weight loss. Weight loss after bariatric surgery is linked to improved glycaemic control in diabetics, including the ability to attain near-normal glycemia without medication or with fewer drugs **(Schofield and Liu, 2016).**

Diet is an important part of controlling metabolic abnormalities in diabetes patients. There is no agreement on the appropriate macronutrient ratio that will assist all diabetic individuals. ADA emphasizes customized nutrition therapy, which takes into account a patient's current eating habit, preferences, and metabolic goals rather than proposing a preset macronutrient distribution. The American Dietetic Association's (ADA) recently released nutrition guidelines do not specify an optimal amount of carbohydrate, protein, or fat to consume, but they do provide specific recommendations for nutritional sources: Carbohydrates should come from vegetables, fruits, whole grains, legumes, and dairy products rather than sources with added fat, sugar, or sodium; leaner protein sources and animal substitutes are favoured. Monounsaturated and polyunsaturated fats, rather than saturated and trans fats, should make up the majority of dietary fat. Moderate alcohol consumption (one drink per day for women and two drinks per day for males) is recommended for those who consume alcohol **(Evert, et al., 2013).** Tree nuts, which are high in polyunsaturated fatty acids, have been demonstrated to lower the risk of cardiovascular events **(Estruch et al., 2013),** possibly through lowering apoB and non-HDL-C levels **(Wu, et al., 2014).**

Nut eating lowered triglycerides and LDL-C in hypertriglyceridemia (>150 mg/dl) participants in a dose-dependent manner, according to a pooled analysis of 25 feeding experiments. Participants with high baseline LDL or low body mass index (BMI), as well as those following a Western diet (as opposed to a Mediterranean or low-fat diet), saw the highest improvement in plasma cholesterol **(Sabate, et al., 2010).** Nuts, in addition to decreasing cholesterol, have a favourable effect on HbA1c in diabetes patients when used as a carbohydrate replacement **(Jenkins, et al., 2011).** Nuts are part of the seed family of foods, which also includes whole grains, legumes, chocolate, and coffee. Seeds are high in macronutrients and micronutrients. Seed eating is linked to a lower incidence of cardiovascular disease and type 2 diabetes. **(Ros and Hu, 2013).**

Dietary fiber is another key component of plant-based meals that helps with glycaemic management and lipid metabolism. However, at realistic levels of consumption, the cholesterol-lowering effect of dietary fiber is limited, and it has only a minor effect on reducing CVD risk. It's difficult to identify the effect of dietary fiber because it can be masked by dietary changes like switching from saturated to unsaturated fatty acids. Many studies have been conducted in order to determine the best food pattern for diabetes people. Low-carbohydrate, low-fat, and Mediterranean diets are among the most researched. A recent meta-analysis of several dietary patterns in the therapy of T2DM found that low-carbohydrate, low-glycaemic index, and low-fat diets were the most effective. When compared to their respective control diets, Mediterranean and high-protein diets all improved glycaemic management, with the Mediterranean diet having the greatest benefit. The Mediterranean and low-carbohydrate diets resulted in more weight loss. Furthermore, low-carbohydrate, low-glycaemic index, and Mediterranean diets all increased HDL by 10%, 5%, and 4%, respectively; all three diets had little effect on LDL, and only the Mediterranean diet reduced triglycerides appreciably. The 20 studies considered employed a variety of control diets, therefore there is no direct comparison between the diets listed above **(Ajala, et al., 2013).**

For weight loss, one study compared the benefits of a low-fat diet with calorie restriction, a Mediterranean diet with calorie restriction, and a low-carbohydrate diet without calorie restriction. The Mediterranean and low carbohydrate diet groups dropped the most weight, although the Mediterranean and low carbohydrate diet groups lost the most. When compared to a low-fat diet, the low-carbohydrate diet improved lipid profile (raising HDL, lowering triglycerides, and lowering the total to HDL cholesterol ratio). Those on the Mediterranean diet had lower fasting plasma glucose levels, which was good news for diabetics. Furthermore, the Mediterranean diet group had the highest reduction in HOMA-IR **(Shai, et al., 2008).** The Mediterranean diet improves various aspects of the metabolic syndrome, such as waist circumference and blood pressure, in addition to lipid and glucose metabolism **(Kastorini, et al., 2011).** Although some dietary patterns appear to be better than others in various ways, there is no single "optimal" dietary pattern for all diabetic individuals in terms of dyslipidaemia management **(Wu and Parhofer, 2014).**

Diet and exercise are two lifestyle changes that can be made. Dietary restriction and physical activity are two aspects of diabetes lifestyle adjustment. Weight loss is one of the benefits of dietary restriction. Caloric restriction is critical in this aspect, and any amount of weight loss is advantageous. In a randomized trial, calorie restriction improved all parameters in obese and overweight people with diabetes, including glycaemic control, HbA1c, and lipid profile **(Rock, et al., 2014).** However, it is uncertain which form of dietary adjustment is best for those with diabetes. Despite the fact that both the ADA **(American Diabetes Association, 2014)** and the Adult Treatment Panel III guidelines prescribe a low-monosaturated-fat diet, new research suggests that a low-carbohydrate diet may be more beneficial. In a study in Spain, individuals who were randomly assigned to a fat-rich Mediterranean diet had a lower risk of CV events and diabetes than those who were recommended to follow a low-fat diet **(Estruch, et al., 2013; Salas, et al., 2014).** Despite the fact that dietary

changes improved various outcomes, no mortality advantage has been proven in diabetes patients. One multicenter randomized controlled trial (Look Action for Health in Diabetes), which randomized overweight and obese diabetics to either calorie restriction and physical activity or usual care, found that while obesity improved, lipid profiles, cardiovascular events, and death did not **(Look, et al., 2013).** Exercise, like nutrition, has been found to improve glycaemic management and lipid profiles; however, no reduction in cardiovascular events or death has ever been demonstrated. **(Warraich and Rana, 2017).**

4. Conclusions

Diabetic dyslipidaemia is very common in T2DM patients (more than 75%). It is typically a mixed (atherogenic) hyperlipidaemia and is a significant CV risk factor. It is characterized by modest increases in LDL-C, elevated TGs, low HDL-C, and small-dense (atherogenic) LDL-C particles, and is usually linked to insulin resistance. As with all dyslipidaemias, statins are the cornerstone of treatment, and the primary goal is to lower LDL-C, as specified in the latest (above-analysed) guidelines. Ezetimibe or even a PCSK9 inhibitor can be administered in a restricted number of instances, such as those with very high LDL-C who are primarily exposed to very high to extreme CVD risk (to the statin). High TGs and low HDL-C contribute to a portion of the modifiable residual CVD risk after statin treatment.

This is the case with a statin-fibrate combination that has been shown to minimize CVD events and improve microvascular consequences of diabetes mellitus (retinopathy, nephropathy, and amputations). Fixed statin-fibrate combos improve patient adherence to medication. Insulin resistance is thought to be the main factor behind the distinctive lipid abnormalities in diabetic dyslipidaemia, which is a common disorder. Hypertriglyceridemia, low HDL cholesterol, and high small dense LDL levels are all related physiologically, with hypertriglyceridemia being the most prominent trait. Diabetic dyslipidaemia can be effectively managed to reduce the risk of CVD. The most essential treatment techniques are lifestyle and pharmaceutical therapies. The most effective way to reduce cardiovascular risk in diabetes patients is to take statins on a regular basis. Though, significant residual risk in statin-treated patients and statin intolerance in some patients still remain an unsolved problem. The role of statin in raising the risk for newly onset diabetes also warrants further research. In the quest for new therapeutic approaches, it is crucial to further promote the understanding of the underlying pathophysiology of lipid abnormalities in diabetic patients and to expand the existing knowledge on already recognised lipid-lowering drugs to clearly identify their role in the management of DD.

5. Recommendations

- All care givers must give vital intellectual directing measures to assist understudies with improving from the effect of diabetic dyslipidaemia.
- Furthermore, health organizations should consider applying the online stages to transfer data on adapting to diabetic dyslipidaemia with the goal that understudies can approach such data.

6. For Further Research

- To reconnoitre the feasibility of virtual training about care of DD.
- To give proposals to exercises that can anticipate understudies' non pharmacological measures for DD.

Abbreviations

Low-density lipoprotein (LDL)-cholesterol (C), cardiovascular disease (CVD), high-density lipoprotein cholesterol (HDL-C), diabetes mellitus (DM), diabetic dyslipidaemia (DD), type 2 diabetes mellitus (T2DM), Type 1 diabetes mellitus (T1DM), triglyceride-rich lipoproteins (TGLs), metabolic syndrome (MetS), very-low density lipoprotein subfraction (VLDL1), insulin resistance (IR), lipoprotein lipase (LPL), cholesterol ester transfer protein (CETP), phospholipid transfer protein (PTP), endothelial lipase (EL), and hepatic lipase (HL), non-alcoholic fatty liver disease (NAFLD), de novo lipogenesis (DNL), diabetic nephropathy (DN), diabetic retinopathy (DR), apolipoprotein B (apoB), free fatty acids (FFA), small-dense low-density lipoprotein (sd-LDL), microsomal triglyceride transfer protein (MTTP), 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), very low-density lipoprotein cholesterol (VLDL), blood pressure (BP), glycated haemoglobin (HbA1c), total cholesterol (TC), non-esterified fatty acids (NEFA), body mass index (BMI).

References

[1] Abbasi A, Corpeleijn E, Gansevoort RT, et al. Role of HDL cholesterol and estimates of HDL particle composition in future development of type 2 diabetes in the general population: the PREVEND study. J Clin Endocrinol Metab. 2013;98:E1352–9.
[2] Abumrad NA, Davidson NO (2012) Role of the gut in lipid homeostasis. Physiol Rev 92:1061–1085 36. Xiao C, Lewis GF (2012) Regulation of chylomicron production in humans. Biochim Biophys Acta 1821:736–746.
[3] Adiels M, Boren J, Caslake MJ, Stewart P, Soro A, Westerbacka J, et al. Overproduction of VLDL1 driven by hyperglycemia is a dominant feature of diabetic dyslipidemia. Arterioscler Thromb Vasc Biol 2005; 25:1697–1703.
[4] ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008 Jun 12;358(24):2560-2572. [doi: 10.1056/NEJMoa0802987] [Medline: 18539916].
[5] Ajala O, English P, Pinkney J. Systematic review and metaanalysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013;97(3):505–16.
[6] American Diabetes Association. 9. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018 Jan;41(Suppl 1):S86-104. [doi: 10.2337/dc18-S009] [Medline: 29222380].

[7] American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care 2014; 37 (Suppl 1):S14–S80.
[8] Arca M, Pigna G, Favoccia C (2012) Mechanisms of diabetic dyslipidemia: relevance for atherogenesis. Curr Vasc Pharmacol 10: 684–686.
[9] Athyros VG, Alexandrides TK, Bilianou H et al (2017) The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk. An expert panel statement. Metabolism 71:17–32.
[10] Athyros VG, Doumas M, Imprialos KP, Stavropoulos K, Georgianou E, Katsimardou A, Karagiannis A. Diabetes and lipid metabolism. Hormones. 2018 Mar;17(1):61-7.
[11] Atmosudigdo IS, Lim MA, Radi B, Henrina J, Yonas E, Vania R, Pranata R. Dyslipidemia increases the risk of severe COVID-19: a systematic review, meta-analysis, and meta-regression. Clinical Medicine Insights: Endocrinology and Diabetes. 2021 Mar;14:1179551421990675.
[12] Beck J, Greenwood DA, Blanton L, Bollinger ST, Butcher MK, Condon JE, 2017 Standards Revision Task Force. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care 2017 Oct;40(10):1409-1419. [doi: 10.2337/dci17-0025] [Medline: 28754780].
[13] Bulut T, Demirel F, Metin A (2017) The prevalence of dyslipidemia and associated factors in children and adolescents with type 1 diabetes. J Pediatr Endocrinol Metab 30(2):181–187
[14] Chehade JM, Gladysz M, Mooradian AD. Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management. Drugs. 2013;73(4):327–39. doi:10.1007/s40265-013-0023-5.
[15] Davis TM, Coleman RL, Holman RR, Group U. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. Circulation. 2013;127:980–7.
[16] Do R, Willer CJ, Schmidt EM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet 2013;45(11):1345–52.
[17] Doucet J, Le Floch JP, Bauduceau B, Verny C (2012) GERODIAB: glycaemic control and 5-year morbidity/mortality of type 2 diabetic patients aged 70 years and older: 1. Description of the population at inclusion. Diabetes Metab 38:523–530.
[18] Emerging Risk Factors Collaboration, N. Sarwar, P. Gao, et al., Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies, Lancet 375 (2010) 2215e2222.
[19] Emerging Risk Factors Collaboration, S.R. Seshasai, S. Kaptoge, A. Thompson, et al., Diabetes mellitus, fasting glucose, and risk of cause-specific death, N Engl J Med. 364 (2011) 829e841.
[20] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013; 368:1279–1290.
[21] Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care 2013;36(11):3821–42.
[22] Faerch K., Carstensen B., Almdal T.P., et al., Improved survival among patients with complicated type 2 diabetes in Denmark: a prospective study (2002e2010), J. Clin. Endocrinol. Metab. 99 (2014) E642eE646.
[23] Ferre P., Foufelle F., Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c, Diabetes Obes. Metab. 12 (Suppl. 2) (2010) 83e92.
[24] Gregg E.W., Li Y., Wang J., et al., Changes in diabetes-related complications in the United States, 1990e2010, N. Engl. J. Med. 370 (2014) 1514e1523.
[25] Guariguata L., Whiting D.R., Hambleton I., et al., Global estimates of diabetes prevalence for 2013 and projections for 2035, Diabetes Res. Clin. Pract. 103 (2014) 137e149.
[26] Hammer SS, Busik JV. The role of dyslipidemia in diabetic retinopathy. Vision research. 2017 Oct 1;139:228-36.
[27] He X, Li J, Wang B, Yao Q, Li L, Song R, et al. Diabetes self-management education reduces risk of all-cause mortality in type 2 diabetes patients: a systematic review and meta-analysis. Endocrine 2017 Mar;55(3): 712-731. [doi: 10.1007/s12020-016-1168-2] [Medline: 27837440].
[28] Hirano T. Abnormal lipoprotein metabolism in diabetic nephropathy. Clin Exp Nephrol. 2014;18(2):206–9. doi:10.1007/s10157-013-0880-y.
[29] Hirano T. Pathophysiology of diabetic dyslipidemia. Journal of atherosclerosis and thrombosis. 2018:RV17023.
[30] Iglay K, Hannachi H, Joseph Howie P, Xu J, Li X, Engel SS, et al. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. Curr Med Res Opin 2016 Jul;32(7):1243-1252. [doi: 10.1185/03007995.2016.1168291] [Medline: 26986190].
[31] Jellinger PS, Handelsman Y, Rosenblit PD et al (2017) American Association of Clinical Endocrinologists and American College of Endocrinology guidelines formanagement of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 23(Suppl 2):1–87.
[32] Jenkins DJ, Kendall CW, Banach MS, et al. Nuts as a replacement for carbohydrates in the diabetic diet. Diabetes Care 2011;34(8):1706–11.
[33] Jensen ET, Dabelea D. Type 2 diabetes in youth: new lessons from the SEARCH study. Curr Diab Rep. 2018;18(6):36.
[34] Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, et al. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med 2014;371(1):32–41.
[35] Joseph J.J., Golden S.H., Type 2 diabetes and cardiovascular disease: what next? Curr. Opin. Endocrinol. Diabetes Obes. 21 (2014) 109e120.
[36] Kastorini CM, Milionis HJ, Esposito K, et al. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and

534,906 individuals. J Am Coll Cardiol 2011;57(11):1299–313.
[37] Kawanami, D., Matoba, K., & Utsunomiya, K. (2016). Signaling pathways in diabetic nephropathy. Renal Replacement Therapy (2016) 2:16 DOI 10.1186/s41100-016-0028-0.
[38] Kershnar AK, Daniels SR, Imperatore G, Palla SL, Petitti DB, Pettitt DJ, et al. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. J Pediatr. 2006;149(3):314–9.
[39] Look ARG, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369:145–154.
[40] Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. Lancet. 2008;371(9626):1800–9.
[41] Parhofer KG. Interaction between glucose and lipid metabolism: more than diabetic dyslipidemia. Diabetes & metabolism journal. 2015 Oct 22;39(5):353-62.
[42] Pelham JH, Hanks L, Aslibekyan S, Dowla S, Ashraf AP. Higher hemoglobin A1C and atherogenic lipoprotein profiles in children and adolescents with type 2 diabetes mellitus. J Clin Translat Endocrinol. 2019;15:30–4.
[43] Petitti DB, Imperatore G, Palla SL, Daniels SR, Dolan LM, Kershnar AK, et al. Serum lipids and glucose control: the SEARCH for diabetes in youth study. Arch Pediatr Adolesc Med. 2007;161(2):159–65.
[44] Rock CL, Flatt SW, Pakiz B, Taylor KS, Leone AF, Brelje K, et al.Weight loss, glycemic control, and cardiovascular disease risk factors in response to differential diet composition in a weight loss program in type 2 diabetes: a randomized controlled trial. Diabetes Care 2014; 37:1573–1580.
[45] Ros E, Hu FB. Consumption of plant seeds and cardiovascular health: epidemiological and clinical trial evidence. Circulation, 2013;128(5):553–65.
[46] Rutledge JC, Ng KF, Aung HH, Wilson DW. Role of triglyceride-rich lipoproteins in diabetic nephropathy. Nat Rev Nephrol. 2010;6(6):361–70. doi:10.1038/nrneph.2010.59.
[47] Sabate J, Oda K, Ros E. Nut consumption and blood lipid levels: a pooled analysis of 25 intervention trials. Arch Intern Med 2010;170(9):821–7.
[48] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9 edition. Diabetes Res Clin Pract 2019 Nov;157:107843. [doi: 10.1016/j.diabres.2019.107843] [Medline: 31518657].
[49] Salas-Salvado J, Bullo M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med 2014; 160:1–10.
[50] Sattar N., Revisiting the links between glycaemia, diabetes and cardiovascular disease, Diabetologia 56 (2013) 686e695.
[51] Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes dyslipidemia. Diabetes therapy. 2016 Jun;7(2):203-19.
[52] Schwarz PE, Timpel P, Harst L, Greaves CJ, Ali MK, Lambert J, et al. Blood sugar regulation for cardiovascular health promotion and disease prevention: JACC health promotion series. J Am Coll Cardiol 2018 Oct 9;72(15):1829-1844 [FREE Full text] [doi: 10.1016/j.jacc.2018.07.081] [Medline: 30286928].
[53] Shah S, Casas JP, Drenos F, et al. Causal relevance of blood lipid fractions in the development of carotid atherosclerosis: Mendelian randomization analysis. Circ Cardiovasc Genet 2013;6(1):63–72.
[54] Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359(3):229–41.
[55] Shaw J.E., Sicree R.A., Zimmet P.Z., Global estimates of the prevalence of diabetes for 2010 and 2030, Diabetes Res. Clin. Pract. 87 (2010) 4e14.
[56] Sherifali D, Bai J, Kenny M, Warren R, Ali MU. Diabetes self-management programmes in older adults: a systematic review and meta-analysis. Diabet Med 2015 Nov;32(11):1404-1414. [doi: 10.1111/dme.12780] [Medline: 25865179].
[57] Sone H, Tanaka S, Tanaka S, Iimuro S, Oida K, Yamasaki Y, Oikawa S, Ishibashi S, Katayama S, Ohashi Y, Akanuma Y, Yamada N, Japan Diabetes Complications Study Group Serum level of triglycerides is a potent risk factor comparable to LDL cholesterol for coronary heart disease in Japanese patients with type 2 diabetes: subanalysis of the Japan Diabetes Complications Study (JDCS). *J Clin Endocrinol Metab*. 2011, 96: 3448-3456.
[58] Song Y, Liu X, Zhu X, Zhao B, Hu B, Sheng X, et al. Increasing trend of diabetes combined with hypertension or hypercholesterolemia: NHANES data analysis 1999-2012. Sci Rep 2016 Nov 2;6:36093 [FREE Full text] [doi: 10.1038/srep36093] [Medline: 27805013].
[59] Sunil B, Ashraf AP. Dyslipidemia in pediatric type 2 diabetes mellitus. Current Diabetes Reports. 2020 Oct;20(10):1-9.
[60] Taskinen MR, Borén J (2015) New insights into the pathophysiology of dyslipidemia in type 2 diabetes. Atherosclerosis 239:483–495.
[61] Tg, Hdl Working Group of the Exome Sequencing Project NHL, Blood I, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med 2014;371(1): 22–31.
[62] Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. J Hypertens 2017 May;35(5):922-944. [doi: 10.1097/HJH.0000000000001276] [Medline: 28141660].

[63] Timpel P, Oswald S, Schwarz PE, Harst L. Mapping the evidence on the effectiveness of telemedicine interventions in diabetes, dyslipidemia, and hypertension: an umbrella review of systematic reviews and meta-analyses. Journal of medical Internet research. 2020 Mar 18;22(3):e16791.
[64] Verges B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia. 2015;58:886–99.
[65] Vijayaraghavan K (2010) Treatment of dyslipidemia in patients with type 2 diabetes. Lipids Health Dis 9:144.
[66] Wang J, Stancakova A, Soininen P et al (2012) Lipoprotein subclass profiles in individuals with varying degrees of glucose tolerance: a population-based study of 9399 Finnish men. J Intern Med 272: 562–572.
[67] Warraich HJ, Rana JS. Dyslipidemia in diabetes mellitus and cardiovascular disease. Cardiovascular Endocrinology. 2017 Mar;6(1):27.
[68] Warraich HJ, Wong ND, Rana JS. Role for combination therapy in diabetic dyslipidemia. Curr Cardiol Rep. 2015;17:32.
[69] Whiting DR, Guariguata L, Weil C et al (2011) 2011 IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 94:311–321.
[70] Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018 Sep 1;39(33):3021-3104. [doi: 10.1093/eurheartj/ehy339] [Medline: 30165516].
[71] Wu L, Parhofer KG. Diabetic dyslipidemia. Metabolism. 2014 Dec 1;63(12):1469-79.
[72] Wu L, Piotrowski K, Rau T, et al. Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: a randomized controlled cross-over clinical trial. Metabolism 2014;63 (3):382–91.
[73] Zhou Y, Wang C, Shi K, Yin X. Relationship between dyslipidemia and diabetic retinopathy: a systematic review and meta-analysis. Medicine. 2018 Sep;97(36).
[74] Zimmet PZ, Magliano DJ, Herman WH et al (2014) Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol 2:56–64.