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Dyslipidemia poses a significant risk of many complications for Type 2 Diabetes Mellitus Patients: Article Review

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A B S T R A C T

The most prevalent chronic illnesses to be identified and treated collectively are dyslipidemias. They are typically identified by triglycerides serum, cholesterol, or both, Atypical levels of related lipoprotein species, including high of very low density lipoproteins VLDL, low HDL cholesterol, high LDL cholesterol, and a predominance of small dense LDL particles, are also present. are all signs of diabetic dyslipidemia. Chronic Kidney disease (CKD) alone may result in dyslipidemia due to disruption of lipids metabolism. Hyperglycemia and insulin resistance may exacerbate dyslipidemia in diabetic patients with CKD. Patients with type 2 diabetes mellitus bear a disproportionately high burden of cardiovascular disease, the primary global origin of morbidity and mortality, with the proportion of CVD attributed to diabetes rising in the general population. A significant microvascular consequence of diabetes is diabetic retinopathy (DR). Among developed countries, it is the most frequent cause of blindness among people of working age. The most prevalent neuropathy, diabetic neuropathy, has a variety of clinical symptoms connected with it. After the age of 50, it typically occurs, and people with long-term diabetes mellitus are more likely to experience it. However, macrovascular pathogenesis is also involved. It begins with microvascular damage to the tiny blood arteries that nourish the nerves. The aim of writing this article is that the imbalance of fats and their high concentrations in the human body of a patient with type 2 diabetes generates many complications, which over time are dangerous complications that threaten the life of a diabetic patient and lead to his death if these complications are not controlled because the high levels of sugar and fat in the human body It plays an important role in the development of the patient's condition.

1. Introduction

The most prevalent chronic illnesses to be identified and treated collectively are dyslipidemias. They are typically identified by aberrant of triglycerides, cholesterol levels or both of them; also different levels of associated lipoprotein species. Increased atherosclerotic cardiovascular disease (ASCVD) risk is the most frequently observed clinical effect of dyslipidemia and is correlated with increased (LDL), (TC),(TGs), and lipoprotein(a) (Lp(a)), as well as decreased high-density lipoprotein (HDL)-C(1). In particular, diabetic and obesity are often occurring secondary risk factors. In persons with genetically impaired synthesis of apolipoprotein, rare dyslipidemias are also associated with deficits in fat-soluble vitamins, hepatosteatosis, and pancreatitis with substantial TG elevations(2). The two plasma lipids that are most clinically important are TGs and cholesterol (Fig. 1). A component of cell membrane, a precursor for the production of steroids hormone, bile acids, and oxysterols, and a modulator of molecules involved in brain signaling, cholesterol performs a number of physiological activities. Adipose and muscle tissue are fueled by TGs. The spherical lipoprotein particles' hydrophobic center, which is shielded from the aqueous plasma by their surface phospholipids and apolipoprotein (3,4), is where cholesterol and TGs circulate. The differences between the lipoprotein species of chylomicrons (CM), (VLDL), (IDL), (LDL), and (HDL) include their functions, sizes, densities, relative lipid contents, and distinctive apolipoproteins. The latter components give the particles stability and can function as transporter molecules, cofactors in processing, and receptor ligands (5).

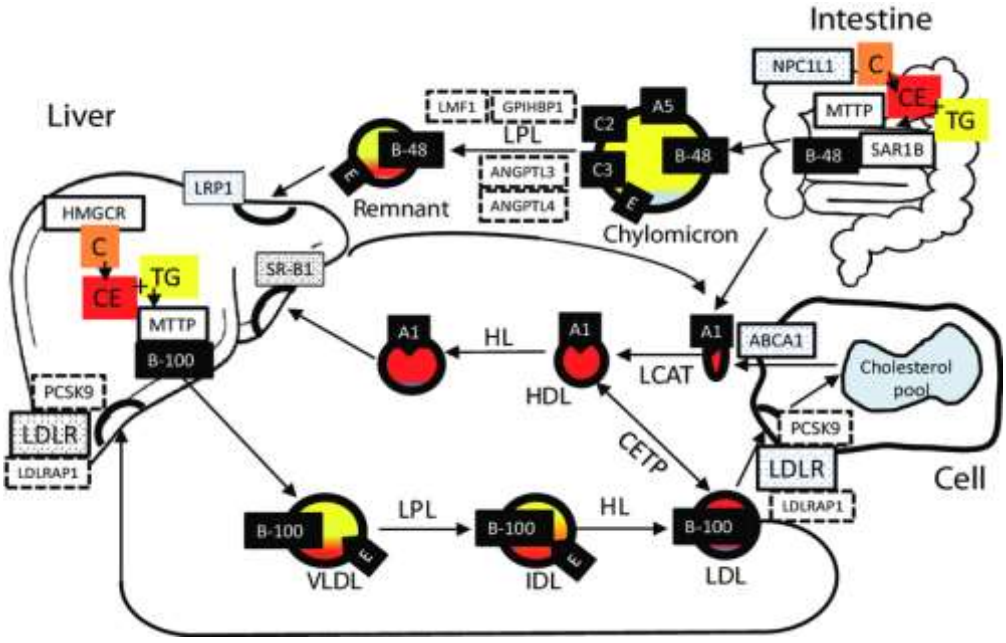

Figure 1. Plasma lipoprotein and lipid metabolism diagram

Plasma lipoprotein metabolism diagram is showed. Abbreviations and full explanations are provided in the text. Red indicates cholesterol ester, orange indicates free cholesterol, yellow indicates TG, black boxes indicate apolipoproteins, stippled boxes indicate receptors or transporters, and dashed box borders indicate auxiliary proteins.(5).

2. Diabetic dyslipidemia:

Insufficient insulin activity causes diabetes, a hyperglycemic condition, but insulin also significantly affects blood lipid levels. In populations with diabetes, changes in serum lipids (dyslipidemia) are frequently observed, regardless of insulin resistance or shortage. There is no question that the most significant risk factor for atherosclerotic cardiovascular disease (CVD), including coronary artery disorders, is low-density lipoprotein (LDL)-cholesterol (C) (6). However, in populations with diabetes, hypertriglyceridemia and low levels of high-

density lipoprotein (HDL-C) are more prevalent than severe hypercholesterolemia. According to a representative cohort research for persons with type 2 diabetes, serum triglyceride (TG) levels are a better predictor of CVD than hemoglobin A1c and are comparable to LDL-C. This finding only suggests that dyslipidemia, especially in diabetic patients with significantly elevated blood glucose levels, is a stronger CVD risk than hyperglycemia. Understanding the pathogenesis of dyslipidemia based on a lack of insulin activity is crucial(7).

High fasting and postprandial triglycerides, low HDL-C, high LDLC, and a predominance of tiny dense LDL-C particles are all signs of diabetic dyslipidemia. The primary association between diabetic and the elevated cardiovascular risk of diabetes people is these lipid alterations. Only a portion of the pathophysiology is understood(8). Due to modifications in insulinsensitive pathways, increased levels of free fatty acids, and excessive production of triglyceride-rich lipoproteins of intestinal and hepatic origin., and low grade inflammation. The differences in HDL and LDL that have been observed are substantially explained by this. Although altering one's lifestyle and managing blood sugar can help lipid profiles, statin medicine has the biggest impact on reducing cardiovascular risk. The majority of diabetic individuals should therefore be prescribed statin medication.. Other medications for decreasing cholesterol, including fibrate, omega-3 fatty acids, niacin, and bile acid sequestrants, have less clear roles since their majority of unfavorable result studies(9).

3. Correlation between dyslipedimia and diabetic nephropathy:

CKD alone may result in dyslipidemia due to disruption of lipids metabolism. Hyperglycemia and insulin resistance may exacerbate dyslipidemia in diabetic patients with CKD. Patients with CKD have lower levels of LPL expression and activity in their endothelial cells. These anomalies may cause the delayed breakdown of triglyceride-rich lipoproteins found in ApoB. The elimination of ApoB would be suppressed and LPL activity would be inhibited by elevated levels of Apo-CIII, which are frequently detected in patients with diabetes microalbuminuria (10). Hepatic lipase has the ability to hydrolyze triglycerides and phospholipids in HDL and chylomicron remnants. Hepatic lipase expression and activity are lowered in CKD, which has been demonstrated in animal. Animals with CKD had reduced levels of LDL receptor-related protein and VLDL-C receptor messenger RNA, according to research (11). Atherogenic chylomicron can result from any of these diseases. and VLDL-C remnant accumulation. Apo-AI levels drop in CKD patients as a result of increased catabolism and decreased hepatic synthesis. Reduced adenosine triphosphate-binding cassette transporter 1 binding affinity, low Apo-AI concentration, and decreased lecithin-cholesterol acyltransferase activity all contribute to a drop in HDL(12). production. LDL-C and total cholesterol readings are often within acceptable ranges. There is growing evidence connecting dyslipidemia to the onset and progression of renal impairment in people with and without diabetes. Dyslipidemia is one of the variables that can cause diabetic nephropathy. For instance, triglyceride-rich lipoprotein may promote the transforming growth factor-beta activation. Following this, TGF- encourages the creation of reactive oxygen species, which results in glomerular injury. The tubulointerstitium and mesangium both experience an increase in matrix deposition as a result of TGF- activation (13). Triglyceride-rich lipoprotein can activate monocytes and disrupt cellular glycocalyx in addition to the TGF- pathway, increasing permeability in the glomerulus (14,15). An increase in monocyte chemoattractant expression, inhibition of NO, and modulation of mesangial cells proliferation are all effects of oxidized lipoprotein that might cause glomerular damage (16). HDL has the power to counteract these negative consequences. However, a lower HDL-C in CKD patients may hasten renal damage. Treatment with lipid-lowering medications may benefit renal outcomes in T2D patients in addition to their positive effects on CVD since diabetic nephropathy may be exacerbated by dyslipidemia(17)..

4. Correlation between dyslipedimia and diabetic cardiovascular disease CVD:

Patient with (T2DM) bears a disproportionately high burden of cardiovascular diseases (CVD), the leading origin of morbidity and mortality worldwide, with the proportion of CVD attributed to diabetes rising in the general population. Reducing the risk of CVD in this population is crucial for public health given the increased prevalence of diabetes overall, especially among ethnic minorities(18). Despite the fact that statins and lifestyle changes are the first-line therapy for lowering the risk of CVD, people with diabetes still have a high risk of having adverse cardiovascular events(19). Still it is the main cause of death in the population, cardiovascular disease (CVD). The high prevalence of risk factors like obesity and (T2DM) is partially responsible for the high incidence of CVD.Being overweight or obese greatly increases the risk of CVD, and having T2DM increases that risk relative to not having the condition (20). People with T2DM still have a higher residual CVD risk even when reducing (LDL) through the use of statins has decreased the incidence of atherosclerotic CVD events.

T2DM is actually associated with metabolic dyslipidemia, a disorder marked by high levels of triglycerides and/or low levels of (HDL-C). The extent to which improvements in the triglyceride-HDL phenotype reduce CVD risk beyond LDL-C is currently unknown. The relationship between metabolic dyslipidemia and incidence CVD in overweight or obese persons with T2DM is also poorly understood(21). Although persons with T2D still have a high risk of cardiovascular events, lifestyle adjustments and The first-line therapies for lowering CVD risk in these people are statins. This continued CVD risk may be brought on by the abnormal metabolism of TRLs, such as chylomicrons, VLDL, and their associated remnant lipoprotein particles (RLPs), many of which are present as intermediate-density lipoproteins(22). As a result, it's important to develop safe and reliable alternatives for preventing and controlling diabetic dyslipidemia. According to a report by Roger et al., a hybrid drug that inhibits both the In a mouse model, the cannabinoid-1 receptor (CB1R) and inducible nitric oxide synthase (iNOS) is described in this issue of Diabetes. (23). Therefore, it may provide a new treatment method to concurrently lower LDL and VLDL levels.

5. Correlation between dyslipedimia and diabetic Retinopathy:

A significant microvascular consequence of diabetes is diabetic retinopathy (DR). Among developed countries, it is the most frequent cause of blindness among people of working age. With the progression of diabetes, DR prevalence rises. After 20 years of diabetes, more than 60% of type 2 patients and practically all type 1 patients develop some degree of retinopathy (24,25). It has been proven that lipids play a role in the development of DR. In the 1950s, Keiding et al. discovered a connection between serum lipid levels and the generation of hard exudates. Additional evidence for it came from studies on dietary lipid therapies (26). Examining blood lipid profiles from samples from the Diabetes Control and Complications Trial (DCCT) revealed a significant correlation between the onset of DR and dyslipidemia in people with type 1 diabetes, which was also supported by a number of clinical trials involving the use of lipid-lowering medications. (27). According to the Fenofibrate Intervention and Event Lowering in Diabetes research, fenofibrate therapy significantly decreased the requirement for DR laser therapy after five years. More particular, delivery of the fenofibrate (clofibrate) prototype, a PPAR activator called clofibrate, led to decreases in hard exudates. Patients with type 2 diabetes who took simvastatin and fenofibrate to reduce their triglyceride and cholesterol levels saw decreased DR advancement after 4 years, according to the Action to Reduce Cardiovascular Risk in Diabetes Eye Study (28, 29).

6. Correlation between dyslipedimia and diabetic neuropathy:

The most prevalent neuropathy, diabetic neuropathy, has a variety of clinical symptoms connected with it. After the age of 50, it typically occurs, and people with long-term diabetes mellitus are more likely to experience it. However, macrovascular pathogenesis is also involved. It begins with microvascular damage to the tiny blood arteries that nourish the nerves. A multitude of multifactorial metabolic problems, such as growth factor insufficiency, hyperglycemia, nitrosative stress, oxidative and dyslipidemia, and, have an impact on the etiology of sensory neuropathy in diabetes mellitus type 2 (30). Advanced glycated end products, the flow of the sorbitol aldose reductase (polyol) pathway, and the activation of the protein kinase C enzyme are a few metabolic products that are hypothesized to aid in the development of neuropathy(31). Because it causes oxidative stress in the sensory neurons of the root ganglia, dyslipidemia significantly contributes to the development of diabetic neuropathy(32). As stated by Fujita et al. metabolic alterations in glucose and lipids (total cholesterol, triglycerides, and free fatty acids) lead to reduced peripheral nerve activity(33). Patients with diabetes mellitus showed improved vibratory feeling with short-term glucose management. The serum cholesterol levels of type 2 diabetic patients with positive and negative sensorimotor neuropathy did not significantly differ, according to a previous study. In type 2 diabetes mellitus, atherolipid indices like (TC/HDL-C), (TC/LDL-C), (TG/HDL-C) and other ratios predict atherosclerosis but not neuropathy(34).

7. Correlation between dyslipidemia and diabetic foot:

Diabetes-related dyslipidemia may result from insulin secretion problems and consequent hyperglycemia. Additionally, regardless of hyperglycemia, obesity and an insulin-resistant condition cause dyslipidemia to develop. A diabetic foot risk classification paradigm was published by the International Diabetic Federation (IDF). These suggestions are meant to protect the diabetic-foot from injury, ulceration. Before entering the very high Risk Category (35), preventative steps can be taken to control the foot in the early Risk Categories of 1,

and 2. this can be accomplished. One of the most serious diabetes consequences is diabetic foot (DF)(36). DF patients have a markedly worse quality of life and a far higher risk of cardiovascular death and amputation. Amputations that result from DF ulcerations also have a significant negative impact on the healthcare system. For instance, only $963 million, or 1.3% of the National Health Service budget, is spent on DF management annually in England. DF extends the hospital stay by around 8 days. According to estimates, management costs would practically triple for every third reduction in the prevalence of DF(37,38).

8. Correlation between dyslipidemia and diabetic Periodontal:

A multifactorial inflammatory NCD called periodontitis causes the tissues supporting the teeth to die. It is the sixth most prevalent illness that affects people, and 10% of adults worldwide are affected by its severe version. In the United States, its milder variants affect over 50% of persons over the age of 30. Even though it is treatable, significant periodontal tissue loss can result in tooth loss if left untreated, This frequently results in masticatory dysfunction and inadequate nutrition. Additionally, there is a decline in prospects for employment, social relationships, and job performance. As a result, periodontitis has a negative effect on quality of life(39).

There is growing evidence from epidemiological and experimental investigations that systemic causes, illnesses, and circumstances may contribute to the development and spread of periodontitis. Social determinants and shared risk factors that influence Genetic and epigenetic variables, acquired risk factors (socioeconomic status, lifestyles, stress, high glucose, cigarette and alcohol use, and dietary habits high in glucose and lipid), medications, microbial dysbiosis, and bacteremias all affect the immune response locally and systemically. (40). Some of the main risk factors for periodontal disease in diabetic patients are the duration of the condition, inadequate dietary intake, smoking, poor oral hygiene habits, and poor metabolic management(41,42). Another potential risk factor is dyslipidemia. According to several research, people with severe periodontitis had higher levels of TC, LDL cholesterol, and triglycerides than people who don't receive periodontal therapy(43,44,45).

References

[1] Tedesco, P., Beraldo, P., Massimo, M., Fioravanti, M.L., Volpatti, D., Dirks, R. and Galuppi, R. (2020) Comparative therapeutic effects of natural compounds against *Saprolegnia* spp. (Oomycota) and *Amyloodinium ocellatum* (*Dinophyceae*). *Front. Vet. Sci*., 7(1) 83.

[1] Amanda J Berberich, Robert A Hegele, A Modern Approach to Dyslipidemia, *Endocrine Reviews*, Volume 43, Issue 4, August 2022, Pages 611–653, https://doi.org/10.1210/endrev/bnab037.

[2] Xi Y, Niu L, Cao N, Bao H, Xu X, Zhu H, Yan T, Zhang N, Qiao L, Han K, Hang G. Prevalence of dyslipidemia and associated risk factors among adults aged≥ 35 years in northern China: a cross-sectional study. BMC Public Health. 2020 Dec;20:1-9.

[3] Hernández-Alcaraz C, Aguilar-Salinas CA, Mendoza-Herrera K, Pedroza-Tobías A, Villalpando S, Shamah-Levy T, Rivera-Dommarco J, Hernández-Ávila M, Barquera S. Dyslipidemia prevalence, awareness, treatment and control in Mexico: results of the Ensanut 2012. salud pública de méxico. 2020 Apr 15;62(2):137-46.

[4] Alzaheb RA, Altemani AH. Prevalence and associated factors of dyslipidemia among adults with type 2 diabetes mellitus in Saudi Arabia. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2020;13:4033.

[5] Hegele RA. Plasma lipoproteins: genetic influences and clinical implications. Nature Reviews Genetics. 2009 Feb;10(2):109-21.

[6] Hirano T. Pathophysiology of diabetic dyslipidemia. Journal of atherosclerosis and thrombosis. 2018 Sep 1;25(9):771-82.

[7] Kothari V, Bornfeldt KE. A new treatment strategy for diabetic dyslipidemia?. Diabetes. 2020 Oct 1;69(10):2061-3.

[8] Wu L, Parhofer KG. Diabetic dyslipidemia. Metabolism. 2014 Dec;63(12):1469-79. doi: 10.1016/j.metabol.2014.08.010. Epub 2014 Aug 29. PMID: 25242435.

[9] Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of type 2 diabetes mellitus. International journal of molecular sciences. 2020 Jan;21(17):6275.

[10] Chen SC, Tseng CH. Dyslipidemia, kidney disease, and cardiovascular disease in diabetic patients. Rev Diabet Stud. 2013 Summer-Fall;10(2-3):88-100. doi: 10.1900/RDS.2013.10.88. Epub 2013 Aug 10. PMID: 24380085; PMCID: PMC4063094.

[11] Hirano T, Satoh N, Kodera R, Hirashima T, Suzuki N, Aoki E, Oshima T, Hosoya M, Fujita M, Hayashi T, Ito Y. Dyslipidemia in diabetic kidney disease classified by proteinuria and renal dysfunction: A cross-sectional study from a regional diabetes cohort. Journal of Diabetes Investigation. 2022 Apr;13(4):657-67.

[12] Kawanami, D., Matoba, K. & Utsunomiya, K. Dyslipidemia in diabetic nephropathy. Ren Replace Ther 2, 16 (2016). https://doi.org/10.1186/s41100-016-0028-0

[13] Su W, Cao R, He YC, Guan YF, Ruan XZ. Crosstalk of hyperglycemia and dyslipidemia in diabetic kidney disease. Kidney diseases. 2017;3(4):171-80.

[14] Găman MA, Dobrică EC, Cozma MA, Antonie NI, Stănescu AM, Găman AM, Diaconu CC. Crosstalk of magnesium and serum lipids in dyslipidemia and associated disorders: a systematic review. Nutrients. 2021 Apr 22;13(5):1411.

[15] Ebrahimpour S, Zakeri M, Esmaeili A. Crosstalk between obesity, diabetes, and alzheimer's disease: Introducing quercetin as an effective triple herbal medicine. Ageing research reviews. 2020 Sep 1;62:101095.

[16] Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. Journal of the formosan Medical Association. 2018 Aug 1;117(8):662-75.

[17] Hung PH, Hsu YC, Chen TH, Lin CL. Recent advances in diabetic kidney diseases: from kidney injury to kidney fibrosis. International Journal of Molecular Sciences. 2021 Nov 1;22(21):11857.

[18] Warraich HJ, Rana JS. Dyslipidemia in diabetes mellitus and cardiovascular disease. Cardiovasc Endocrinol. 2017 Feb 15;6(1):27-32. doi: 10.1097/XCE.0000000000000120. PMID: 31646116; PMCID: PMC6768535.

[19] Bhatt D, Steg G, Miller M, Brinton E, Jacobson T, Ketchum S, Doyle R, Juliano R, Jiao L, Granowitz C. Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial—REDUCE-IT. N. Engl. J. Med. 2019 Mar;380:11-22.

[20] Kaze AD, Santhanam P, Musani SK, Ahima R, Echouffo-Tcheugui JB. Metabolic dyslipidemia and cardiovascular outcomes in type 2 diabetes mellitus: findings from the look AHEAD study. Journal of the American Heart Association. 2021 Apr 6;10(7):e016947.

[21] BenjaminEJ, MuntnerP, AlonsoA, BittencourtMS, CallawayCW, CarsonAP, ChamberlainAM, ChangAR, ChengS, DasSR, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139:e56–e528. DOI: 10.116

[22] Kothari V, Bornfeldt KE. A new treatment strategy for diabetic dyslipidemia?. Diabetes. 2020 Oct 1;69(10):2061-3.

[23] Roger C, Buch C, Muller T, Leemput J, Demizieux L, Passilly-Degrace P, Cinar R, Iyer MR, Kunos G, Vergès B, Degrace P. Simultaneous inhibition of peripheral CB1R and iNOS mitigates obesity-related dyslipidemia through distinct mechanisms. Diabetes. 2020 Oct 1;69(10):2120-32.

[24] Chang YC, Wu WC. Dyslipidemia and diabetic retinopathy. Rev Diabet Stud. 2013 Summer-Fall;10(2-3):121-32. doi: 10.1900/RDS.2013.10.121. Epub 2013 Aug 10. PMID: 24380088; PMCID: PMC4063092.

[25] Hammer SS, Busik JV. The role of dyslipidemia in diabetic retinopathy. Vision Res. 2017 Oct;139:228-236. doi: 10.1016/j.visres.2017.04.010. Epub 2017 May 26. PMID: 28545981; PMCID: PMC5702582.

[26] Ezhilvendhan K, Sathiyamoorthy A, Prakash BJ, Bhava BS, Shenoy A. Association of dyslipidemia with diabetic retinopathy in Type 2 diabetes mellitus patients: A hospital-based study. Journal of Pharmacy & Bioallied Sciences. 2021 Nov;13(Suppl 2):S1062.

[27] Chou, Y., Ma, J., Su, X. et al. Emerging insights into the relationship between hyperlipidemia and the risk of diabetic retinopathy. Lipids Health Dis 19, 241 (2020). https://doi.org/10.1186/s12944-020-01415-3

[28] Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent effects of intensive glycemic control on retinopathy in type 2 diabetes in the action to control cardiovascular risk in diabetes (ACCORD) follow-on study. Diabetes Care. 2016 Jul 1;39(7):1089-100.

[29] Rao H, Jalali JA, Johnston TP, Koulen P. Emerging roles of dyslipidemia and hyperglycemia in diabetic retinopathy: molecular mechanisms and clinical perspectives. Frontiers in Endocrinology. 2021 Mar 22;12:620045.

[30] Al-Ani FS, Al-Nimer MS, Ali FS. Dyslipidemia as a contributory factor in etiopathogenesis of diabetic neuropathy. Indian J Endocrinol Metab. 2011 Apr;15(2):110-4. doi: 10.4103/2230-8210.81940. PMID: 21731868; PMCID: PMC3124996.

[31] Jaafar AK, Paulo-Ramos A, Lambert G, Meilhac O, Bourane S. Impact of dyslipidemia on peripheral neuropathy. Atherosclerosis. 2022 Aug 1;355:31-2.

[32] Ali HA, Al Adl AS. Study the role of dyslipidemia in cases of neuropathy with type 2 diabetes mellitus. Al-Azhar Assiut Medical Journal. 2021 Jan 1;19(1):143-51.

[33] Fujita Y, Fukushima M, Suzuki H, Taniguchi A, Nakai Y, Kuroe A, Yasuda K, Hosokawa M, Yamada Y, Inagaki N, Seino Y. Short-term intensive glycemic control improves vibratory sensation in type 2 diabetes. Diabetes research and clinical practice. 2008 Apr 1;80(1):e16-9.

[34] Perez-Matos, M. C., Morales-Alvarez, M. C., & Mendivil, C. O. (2017). Lipids: a suitable therapeutic target in diabetic neuropathy?. Journal of diabetes research, 2017.

[35] AbdAllah AM, Sharafeddin M. Lipid Profile Disorders And Diabetic Foot Risk; Is There A relationship between Them?. Zagazig University Medical Journal. 2022 Nov 1;28(6.1):217-25.

[36] Vujčić S, Stefanović T, Zeljković A, Mihajlović M, Vekić J. Biomarkers of dyslipidemia in patients with diabetic foot. Arhiv za farmaciju. 2022;72(2):184-92.

[37] American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44:S15-S33

[38] Kerr M, Barron E, Chadwick P, Evans T, Kong W, Rayman G, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med. 2019;36(8):995-1002

[39] Bitencourt, F.V.; Nascimento, G.G.; Costa, S.A.; Orrico, S.R.P.; Ribeiro, C.C.C.; Leite, F.R.M. The Role of Dyslipidemia in Periodontitis. *Nutrients* 2023, *15*, 300. https://doi.org/10.3390/nu15020300.

[40] Kapila YL. Oral health's inextricable connection to systemic health: Special populations bring to bear multimodal relationships and factors connecting periodontal disease to systemic diseases and conditions. Periodontology 2000. 2021 Oct;87(1):11-6.

[41] Jiménez-Corona M, Falcón-Flores J, Borges-Yáñez A, Castrejón-Pérez R, Jiménez-Corona A. Dyslipidemia and severe periodontitis among patients with type 2 diabetes. Salud Pública de México. 2021 Mar 4;63(3 May-Jun):331-2.

[42] Zhang D, Zhao C, Liu Z, Ding Y, Li W, Yang H, Wang Z, Li Y. Relationship between periodontal status and dyslipidemia in patients with type 2 diabetic nephropathy and chronic periodontitis: A cross-sectional study. Journal of Periodontal Research. 2022 Oct;57(5):969-76.

[43] Thomas B, Prasad RB, Shetty S, Vishakh R. Comparative evaluation of the lipid profile in the serum of patients with type II diabetes mellitus and healthy individuals with periodontitis. Contemporary Clinical Dentistry. 2017 Jan;8(1):96.

[44] Verhulst MJ, Teeuw WJ, Gerdes VE, Loos BG. Self-reported oral health and quality of life in patients with type 2 diabetes mellitus in primary care: a multi-center cross-sectional study. Diabetes, metabolic syndrome and obesity: targets and therapy. 2019 Jun 18:883-99.

[45] Kapila YL. Oral health's inextricable connection to systemic health: Special populations bring to bear multimodal relationships and factors connecting periodontal disease to systemic diseases and conditions. Periodontology 2000. 2021 Oct;87(1):11-6.