International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Systematic Review on the Impact of Cholesterol Levels on Diabetes Mellitus

M. A. Jebish[1], W. E. Blessy[2]

[1,2]Interns, Doctor of Pharmacy, The Erode College of Pharmacy, TamilnNadu.

ABSTRACT

Diabetes mellitus (DM) is a common metabolic disorder characterized by defects in insulin secretion and action, or both, resulting in chronic hyperglycemia and altered metabolism of carbohydrates, fats, and proteins. In the absence of the major risk factors, diabetes is associated with increased morbidity and mortality from cardiovascular disease. The prevalence of diabetes is 10.1 crores, as per the Indian Council of Medical Research – India Diabetes (ICMR INDIAB) study published in 2023. Serum lipid abnormalities (dyslipidemia) are commonly seen in diabetic populations, irrespective of insulin deficiency or insulin resistance. When insulin activity is very low, it severely inhibits lipoprotein lipase production, which significantly impairs the digestion of triglyceride-rich lipoproteins. As a result, there is an increase in triglyceride-rich lipoproteins and a delay in the clearance of chylomicrons and VLDL. Additionally, insulinopenia leads to a substantial increase in lipolysis in adipose tissue, causing the release of free fatty acids into the bloodstream. This higher supply of fatty acids to the liver improves triglyceride synthesis in the liver, ultimately resulting in increased production and secretion of VLDL. By lowering serum cholesterol with statins, which inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis, decreases the risk of CHD.

Keywords: Diabetes Mellitus, Cholesterol, Statins

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia and disturbances in carbohydrate, protein, and fat metabolism. It results from defects in insulin secretion, insulin action, or both, and is influenced by various causative factors[1]. The association of DM with dyslipidaemias is strongly related to the duration of the disease and glycaemic control[2]. Dyslipidaemias, the major cause of increased mortality and morbidity in diabetic patients, make them more susceptible to coronary artery disease (CAD)[3]. In 2010, the global prevalence of diabetes among adults was estimated to be 6.4%, affecting 285 million people. By 2030, it is expected to increase to 7.7%, affecting 439 million people[4]. In diabetes, dyslipidemia commonly manifests as raised low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C) levels, or elevated triglyceride (TG) levels[5]. Diabetes mellitus is compared among different classes, including type 1, type 2, gestational diabetes, and other types, in terms of diagnostic criteria, etiology, and genetics[6].

ETIOLOGY

Type 1 Diabetes Mellitus

It is mainly due to an autoimmune destruction of the pancreatic β cells through T-cell mediated inflammatory response (insulitis) as well as a humoral (B cell) response[7].

Type 2 Diabetes Mellitus

Due to defects in the function of these cells, the increased demand for insulin could not be met by the pancreatic β cells[8].

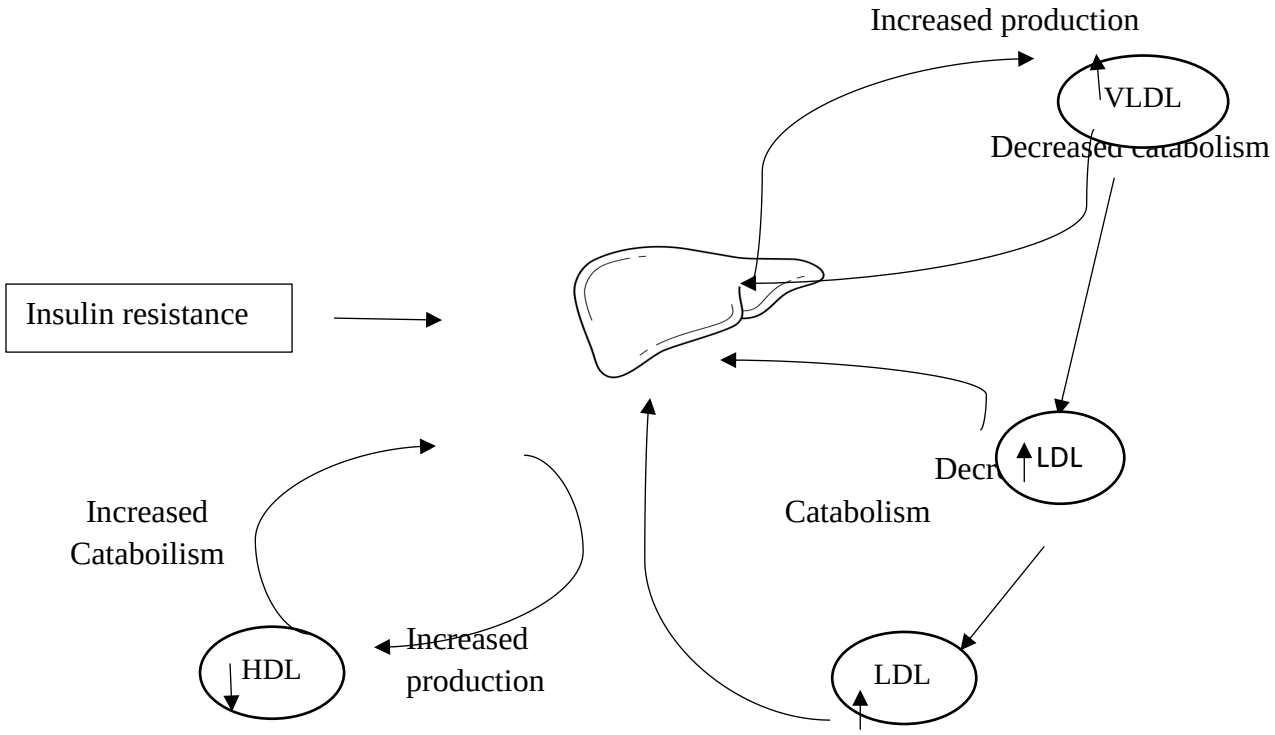
TYPE 1 DIABETES MELLITUS

This type of diabetes is due to the destruction of β cells of the pancreas and constitutes 5%-10% of subjects diagnosed with diabetes[9]. Type 1 diabetes accounts for 80%-90% of diabetes in children and adolescents[10]. In 2013, according to the International Diabetes Federation (IDF), the number of youth (0-14 years) diagnosed with type 1 diabetes worldwide was 497,100 and the number of newly diagnosed cases per year was 78900[11]. The presence of autoantibodies against the pancreatic islet cells is the hallmark of type 1 diabetes, even though the role of these antibodies in the pathogenesis of the disease is not clear[12]. These autoantibodies include islet cell autoantibodies, and autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), protein tyrosine phosphatase (IA2 and IA2β), and zinc transporter protein (ZnT8A). These pancreatic autoantibodies, characteristics of type 1 diabetes, could be detected in the serum of these patients months or years before the onset of the disease[13]. Type 1 diabetes often develops suddenly and can produce symptoms such as polydipsia, polyuria, polyphagia, sudden weight loss, enuresis, lack of energy, extreme tiredness, slow-healing wounds, recurrent infections, and blurred vision with severe dehydration and diabetic ketoacidosis in children and adolescents[14].

TYPE 2 DIABETES MELLITUS

Increased insulin resistance in type 2 diabetes patients raises the demand for insulin in insulin-target tissues. Conversely, insulin secretion decreases over time as the demand for insulin increases, primarily due to the gradual destruction of β cells[15]. Dependence on insulin is one of the major differences between type 1 and type 2 diabetes. Other distinctions include the absence of ketoacidosis in most type 2 diabetes patients, and autoimmune destruction of β cells doesn't occur in type 2 diabetes. While both types have a genetic predisposition, it is stronger in type 2, but the genes are more characterized in type 1[16]. Due to the mild symptoms of type 2 diabetes in the beginning, its diagnosis is often delayed for years, particularly in countries where routine checkups without symptoms are not common. This delay in diagnosis can lead to an increased incidence of long-term complications in type 2 diabetes patients, as hyperglycemia remains untreated during this undiagnosed period. In addition to diabetes, insulin resistance manifests in various ways, including obesity, nephropathy, essential hypertension, dyslipidemia (characterized by hypertriglyceridemia, low HDL, decreased LDL particle diameter, enhanced postprandial lipemia, and remnant lipoprotein accumulation), ovarian hyperandrogenism, premature adrenarche, non-alcoholic fatty liver disease, and systemic inflammation[17].

PATHOPHYSIOLOGY



LIPID LEVELS ON DIABETES

In recent years, it has been recognized that lipid changes may not only result from impaired glucose metabolism but also contribute to it. Hypertriglyceridemia and low HDL-C play a crucial role in this context. Elevated triglyceride levels can lead to increased free fatty acids, which might induce insulin resistance and β-cell dysfunction[18]. It appears that elevated concentrations of free fatty acids disrupt or modulate the cascade connecting insulin receptors with glucose transporters and impede the normal function of the β-cell[19]. Moreover, free fatty acids serve as significant modulators of inflammation. Consequently, hypertriglyceridemia can trigger subclinical inflammation, which subsequently results in insulin resistance and β-cell dysfunction. More recently it was shown that also HDL may directly affect glucose metabolism[20]. HDL facilitates reverse cholesterol transport, and the modified intracellular lipid environment is thought to decrease micro-inflammation. Additionally, the direct anti-inflammatory properties of HDL may also contribute to this process.

STATINS IN THE MANAGEMENT

The cornerstone of treatment for diabetic dyslipidemia is therapeutic lifestyle change.In addition to these measures, recent clinical trials have demonstrated the benefits of statin therapy[21].Therapy with 3-hydroxy-3-methylglutaryl (HMG) Co-reductase inhibitor (statins) in both the Heart Protection Study (HPS) and the Collaborative Atorvastatin Diabetes Study (CARDS) has shown that there is a clear reduction in cardiovascular events in type 2 diabetes[22]. Statin therapy is the mainstay of treatment to reduce ASCVD by decreasing LDL-C by 30%-49% or at least 50% depending on risk level. In 2013, the American College of Cardiology (ACC)/American Heart Association (AHA) published guidelines for the management of cholesterol to reduce ASCVD. The ACC/AHA recommended that any patient with diabetes mellitus type 1 or 2 aged 40-75 should be treated with moderate-intensity statins with a goal

reduction in LDL-C of 30%-49%[23]. High-intensity statins were recommended if the 10-year CV risk score is ≥ 7.5% or if ASCVD was present, with a target LDL-C reduction of ≥ 50%[24].

CONCLUSION

The initial therapy for hypertriglyceridemia includes lifestyle intervention, such as weight loss, increased physical activity, restricted intake of saturated fats, incorporation of monounsaturated fats, reduction of carbohydrate intake, and reduction of alcohol consumption, which may be a risk factor for CVD in people with diabetes. By lowering serum cholesterol with statins, which inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis, decreases the risk of CHD.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

The author would be like to thank guides and driends for valuable guidance for preparing this manuscript.

COMPETING INTERESTS

Authors have declared that no compeing interests exist.

REFERENCES

1. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: WHO; 1999.
2. Windler E. What is the consequence of an abnormal lipid profile in patients with Type 2 diabetes or the metabolic sundrome? Atheroscler Suppl. 2005;6:11-4.
3. Toto RD. Heart disease in diabetic patients. Semin Nephrol. 2005;25:372-8.
4. Mithal A, Majhi D, Shunmugavelu M, Talwarkar PG, Vasnawala H, Raza AS. Prevalence of dyslipidemia in adult Indian diabetic patients: A cross sectional study (SOLID). Indian J Endocrinol Metab. 2014 Sep;18(5):642-7. doi:10.4103/2230-8210.139220. PMID: 25285280; PMCID: PMC4171886.
5. Ethnicity and cardiovascular disease. The incidence of myocardial infarction in white, South Asian, and Afro-Caribbean patients with type 2 diabetes (U.K. Prospective Diabetes Study 32) *Diabetes Care*. 1998;21:1271–7.
6. Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World J Diabetes. 2015 Jun 25;6(6):850-67. doi: 10.4239/wjd.v6.i6.850. PMID: 26131326; PMCID: PMC4478580.
7. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. BMJ. 2004 Mar 27;328(7442):750-4. doi: 10.1136/bmj.328.7442.750. PMID: 15044291; PMCID: PMC381328.
8. Halban PA, Polonsky KS, Bowden DW, Hawkins MA, Ling C, Mather KJ, Powers AC, Rhodes CJ, Sussel L, Weir GC. β-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. Diabetes Care. 2014 Jun;37(6):1751-8. doi: 10.2337/dc14-0396. Epub 2014 May 8. PMID:

9. 24812433; PMCID: PMC4179518.
10. Daneman D. Type 1 diabetes. Lancet. 2006;**367**:847–858.
11. 10. Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatr Diabetes. 2009;**10 Suppl 12**:3–12.
12. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium:International Diabetes Federation; 2013.
13. Vermeulen I, Weets I, Asanghanwa M, Ruige J, Van Gaal L, Mathieu C, Keymeulen B, Lampasona V, Wenzlau JM, Hutton JC, et al. Contribution of antibodies against IA-2β and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. Diabetes Care. 2011;**34**:1760–1765.
14. Couper J, Donaghue KC. Phases of diabetes in children and adolescents. Pediatr Diabetes. 2009;**10 Suppl 12**:13–16.
15. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013.
16. Druet C, Tubiana-Rufi N, Chevenne D, Rigal O, Polak M, Levy-Marchal C. Characterization of insulin secretion and resistance in type 2 diabetes of adolescents. J Clin Endocrinol Metab. 2006;**91**:401–404.
17. Saadi H, Nagelkerke N, Carruthers SG, Benedict S, Abdulkhalek S, Reed R, Lukic M, Nicholls MG. Association of TCF7L2 polymorphism with diabetes mellitus, metabolic syndrome, and markers of beta cell function and insulin resistance in a population-based sample of Emirati subjects. Diabetes Res Clin Pract. 2008;**80**:392–398.
18. Kraemer FB, Ginsberg HN. Gerald M. Reaven, MD: Demonstration of the central role of insulin resistance in type 2 diabetes and cardiovascular disease. Diabetes Care. 2014;**37**:1178–1181.
19. Briaud I, Harmon JS, Kelpe CL, Segu VB, Poitout V. Lipotoxicity of the Pancreatic beta-cell is associated with glucose-dependent esterification of fatty Acids into neutral lipids. Diabetes, 2001;50:315-321.
20. Racheck LI. Free fatty acids and skeletal muscle insulin resistance. Prog Mol Biol Transl Sci. 2014;121-292.
21. Drew BG, Rye KA, Duffy SJ, Barter P, Kingwell BA. The emerging role of HDL in glucose metabolism. Nat Rev Endocrinol. 2012; 8:237-245.
22. Collins R, Aemitage J, Parish S, et al. MRC/BHF heart protection study of Cholesterol-lowering with simvastatin in 5963 people with diabetes: a Randomised placebo-controlled trial. Lancet. 2003;361:2005-2016.
23. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of Cardiovascular disease with Atorvastatin in type II diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo- Controlled trial. Lancet. 2004;364:685-696.
24. Jialal I, Singh G. Management of diabetic dyslipidemia: An update. World J Diabetes. 2019 May 15;10(5):280-290. Doi 10.4239/wjd.v10.i5280. PMID: 31139315; PMCID: PMC6522756.
25. Stone NJ, Robinson JG, Lichtenstein AH, Baiery Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce Atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889-2934.