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

M. A. Jebish¹, W. E. Blessy²

¹²Interns, Doctor of Pharmacy, The Erode College of Pharmacy, TamilNadu.

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 78,900[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.

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COMPETING INTERESTS
Authors have declared that no competing interests exist.

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