Dyslipidemia And Nephropathy In Diabetes Mellitus: A Review

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ABSTRACT

The prolonged increase of blood glucose give rise to complications of diabetes- premature atherosclerosis (including cardiovascular diseases and stroke), retinopathy, nephropathy and neuropathy. The lipid abnormality (dyslipidemia) associated with type 2 diabetes predominantly consists of elevated triglycerides and decreased HDL cholesterol levels. The incident of dyslipidemia in male is higher in comparison to female type 2 diabetic patients. It was also observed that type 2 diabetic patients with higher BMI has higher chance of developing dyslipidemia. Diabetic nephropathy is one of the main microvascular complication of diabetes. In diabetic subjects, a major cause of morbidity and mortality is diabetic nephropathy (DN). Diabetic patients are in risk for the development of dyslipidemia and Diabetic nephropathy. Hyperglycemia causes lipid derangement and nephropathy. Elevated levels of serum cholesterol, triglycerides and lipoproteins are the main lipid derangements in diabetes which are common risk factor for coronary artery disease. It is found that elevated blood glucose levels and duration of diabetes are responsible for nephropathy and microalbuminuria. However Apo B and Lp(a) increases in the microalbuminuria and macroalbuminuria respectively.

KEYWORDS:
Diabetes mellitus, diabetic nephropathy, microalbuminuria, apolipoprotein.

INTRODUCTION:

Diabetes mellitus (DM) is a disease in which the hallmark feature is elevated blood glucose concentrations due to loss of insulin-producing pancreatic β-cells (type 1 diabetes) or through loss of insulin responsiveness in its target tissues (type 2 diabetes). Different studies have described diabetes as one of the main threat to human health in the 21st century (1). Diabetes mellitus is one of the commonest chronic disease globally and number of diabetic patients is increasing day by day (2). In 2021, it is evaluated that 537 million people have diabetes and this figure is expected to reach 643 million by 2030, and 783 million by 2045. It is also found that above 6.7 million people aged 20-79 will die due to causes associated to diabetes (3).

There are at least two major identifiable pathological defects in patients with type 2 diabetes. One is decreased ability of insulin to act on the peripheral tissue. This is called insulin resistance. The other is β-cell dysfunction, which is an inability of the pancreas to produce sufficient insulin to compensate for the insulin resistance. Thus, there is a relative deficiency of insulin early in the disease and absolute insulin deficiency later in the disease. Type 2 diabetes is an extremely heterogeneous disease and no single cause is adequate to explain the progression from normal glucose tolerance to diabetes (4). Type 2 diabetes mellitus has a higher genetic link than type 1 DM, the pathogenesis of type 2 diabetes mellitus is characterized by decreased insulin secretion and insulin resistance (5).

Figure 1: Pathogenesis of type 2 diabetes characterized by impaired insulin secretion and insulin resistance.
Diabetes can be diagnosed on the basis of plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or A1C criteria. (6)

Table 1
Criteria for the diagnosis of diabetes

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<tr>
<td>FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*</td>
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<tr>
<td>Or</td>
<td>2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*</td>
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<tr>
<td>Or</td>
<td>A1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT (Diabetes Control and Complications Trial) assay.*</td>
</tr>
<tr>
<td>Or</td>
<td>In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).*</td>
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</table>

*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

The prolonged increase of blood glucose give rise to complications of diabetes- premature atherosclerosis (including cardiovascular diseases and stroke), retinopathy, nephropathy and neuropathy (7).

Dyslipidemia in type 2 diabetes

The American Diabetes Association (ADA) has set desirable LDL cholesterol, HDL cholesterol, and triglyceride levels as less than 100 mg/dl, more than 40 mg/dl in men/more than 50 mg/dl in women, and less than 150 mg/dl, respectively. (8) The dyslipidemia related with type 2 diabetes generally consists of increased triglycerides and lowered HDL (high density lipoprotein) cholesterol level (9) with a dominance of small dense LDL (Low density lipoprotein) cholesterol (10). The level of LDL cholesterol in type 2 diabetic patients is usually not remarkably different from non-diabetic individuals. (11)

By influencing several factors, insulin resistance may play a major role in the occurrence of diabetic dyslipidemia. In insulin resistance and type 2 diabetes, increased outflow of free fatty acids from adipose tissue and decreased insulin mediated skeletal muscle uptake of free fatty acids causes increase fatty acid inflow to the liver (10) which in turn stimulates the secretion of apolipoprotein B (ApoB) and VLDL cholesterol. The insulin’s decreased ability to inhibit release of free fatty-acid leads to increased hepatic VLDL cholesterol production, which correlates with the extent of hepatic fat accumulation. The elevated concentration of VLDL cholesterol particles and elevated triglyceride concentration in plasma lowers the level of HDL cholesterol and increases the concentration of small dense LDL-cholesterol particle through various processes: VLDL-transported TG (triglyceride) is interchanged with HDL-transported cholesterol ester by the activity of the cholesteryl ester transfer protein (CEPT), which causes in increased concentration of of both atherogenic cholesterol-rich VLDL remnant particles and triglycerides-rich, cholesterol-less HDL particles. The HDL cholesterol which has higher concentration of triglycerides is hydrolyzed by hepatic lipase or lipoprotein lipase which result in dissociation of ApoA-I from the decreased-size HDL. The ApoA-I is filtered by the renal glomeruli and break down in renal tubular cells. The elevated level of small dense LDL-cholesterol particles is explained by a similar lipid exchange. Increased concentration of VLDL-carried triglyceride enable CETP to stimulate the transfer of triglyceride into LDL in exchange for LDL-carried cholesteryl ester. The LDL which is rich in triglyceride is hydrolyzed by hepatic lipase or lipoprotein lipase, which gives lipid-depleted small dense LDL particles. (12)

Figure 2: depicts the role of insulin resistance in diabetic dyslipidemia.

Insulin resistance begin the feature of triad of elevated triglyceride levels, low HDL cholesterol level and high small dense LDL level. Insulin resistance found to contribute either directly or indirectly to the triad of plasma lipid abnormalities of diabetes mellitus, called as hypertriglyceridemia, low HDL-cholesterol levels and high small dense LDL-cholesterol levels. (12) Increased serum levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C) are strongly linked with increased risk for macrovascular
events (e.g., myocardial infarction, ischemic stroke, and coronary mortality) in patients with T2DM.(13)

**Diabetic Nephropathy and microalbuminuria**

Diabetic nephropathy (DN) is one of the commonest microvascular complications of diabetes. In diabetic subjects, a major cause of morbidity and mortality is diabetic nephropathy (DN). It is a main cause of end-stage renal disease (ESRD), and its prevalence is progressively increasing worldwide. (1) DN appears in both type 1 and type 2 diabetes and is found in about 5-10% of patients who suffer from non insulin dependent diabetes (NIDD). In spite of this relatively low occurrence in type 2 diabetes, those patients have been widely studied, since type 2 is far more common than type 1. Classically the development of DN depends mainly on the duration of diabetes; however modern theory believe that the pathogenesis of DN is multi-factorial. In addition to chronic hyperglycemia, the major cause which initiates factors and mediators of diabetic renal disease, hypertension, dyslipidemia and obesity have to be risk factors and to be related for differences in onset and severity of renal disease among diabetic patients. (1)

The initial sign of ongoing nephropathy is microalbuminuria (MA), which is defined as urinary excretion of albumin at the rate of 30-299 mg/24hrs or 20-199 μg/min. if microalbuminuria is present it indicate worsening of renal disease to overt diabetic nephropathy (14). Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide, and it is estimated that 20% of type 2 diabetic patients reach ESRD during their lifetime. (15)

Multiple biochemical mechanisms by which diabetes causes diabetic nephropathy have been proposed to explain the adverse effect of hyperglycemia, including inappropriate activation of the protein kinase C (PKC)–mitogen-activated protein kinase (MAPK) pathway, activation of the polyol pathway, increased accumulation of advanced glycation end products, and oxidative stress. (16)

The initial clinical proof of nephropathy is the excretion of low but abnormal levels (≥30 mg/day or 20 μg/min) of albumin in the urine, called as microalbuminuria, and patients with microalbuminuria are said to have incipient nephropathy. A larger number of type 2 diabetes patients are found to have microalbuminuria and overt nephropathy shortly after the diagnosis of their diabetes, as these individuals may be suffering from diabetes for many years before the diagnosis is made and also because the presence of albuminuria may be less specific for the presence of diabetic nephropathy, as indicated by biopsy studies. If there is no specific interventions, 20–40% of type 2 diabetic patients with microalbuminuria lead to overt nephropathy, but by 20 years after development of overt nephropathy, only ~ 20% will have worsen to ESRD (end stage renal disease). (17) Furthermore, microalbuminuria being the earliest indication of nephropathy, albuminuria is a indicator of remarkably increased cardiovascular morbidity and mortality for patients with either type 1 or type 2 diabetes.

Thus, the finding of microalbuminuria is an signal for screening for probable vascular disease and aggressive intervention to minimize all cardiovascular risk factors (e.g., lowering of LDL cholesterol, antihypertensive therapy, cessation of smoking, institution of exercise, etc.). Additionally, it is found that lowering of cholesterol may decrease the degree of proteinuria. (17)

<table>
<thead>
<tr>
<th>Category</th>
<th>Spot collection (μg albumin/ mg creatinine)</th>
<th>24-h collection (mg/24 h)</th>
<th>Timed collection (μg/min)</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–299</td>
<td>30–299</td>
<td>20–199</td>
</tr>
<tr>
<td>Clinical albuminuria</td>
<td>≥300</td>
<td>≥300</td>
<td>≥200</td>
</tr>
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If urinary albumin excretion is ≥30 mg/24h (equivalent to 20μg /min on a timed specimen or 30 mg/g creatinine on a randomsample) it is called as microalbuminuria. (17) A Study on Lipid Profile Levels of Diabetics and Non-Diabetics Among Naini Region of Allahabad, India and found that Hypercholesterolemia, Hypertriglyceridaemia and lipoprotein are the main lipid abnormalities found in diabetes which is risk for coronary artery disease. In diabetes sex plays a significant effect on risk of coronary artery disease. (18). In another study of 355 type 2 diabetic patient, it was found that occurrence of dyslipidemia is high and dyslipidemia was present in 224 (63%) patient. It was also observed that incident of dyslipidemia in male is higher in comparison to female patients. They also observed that patients with higher BMI has higher chance of developing dyslipidemia. (19) However the effect of gender on dyslipidemia in patients with DM remains controversial, different studies conducted in
different countries reported a higher incidence of dyslipidemia in females compared to males. Hyperlipidemia in females may be due to the effects of estrogen on body fat distribution, which results in differences in altered lipoproteins.\(^{(20)}\)

Arnaud et al. in their study on 4199 obese adults with DM who do not have CVD and analyzed link of triglycerides HDL-C status with several CVD outcomes. In DM patients dyslipidemia was common (40%). It was also found that low HDL-C and metabolic dyslipidemia were connected with raised risks of CAD (coronary artery disease).\(^{(21)}\)

The prevalence of overt nephropathy and microalbuminuria was 2.2 and 26.9%, respectively \(^{(22)}\). There are number of responsible factors for CKD progression, found specific relationship among inflammatory chemokines and progression of diabetic CKD.\(^{(23)}\) Duration of diabetes, Hb A\(_{1C}\) and systolic blood pressure were the common risk factors for overt nephropathy and microalbuminuria.\(^{(22)}\) glycemic control but not lipids were associated with abnormal urinary albumin excretion, a marker of increased risk for progressive disease.\(^{(24)}\) Elevated levels of Apo B & Lp (a) was found in the stages of microalbuminuria and macroalbuminuria respectively. Throughout the 3 stage of albuminuria, triglycerides increases significantly.\(^{(25)}\)

**CONCLUSION:**

Diabetic patients are in risk for the development of dyslipidemia and Diabetic nephropathy. Hyperglycemia causes lipid derangement and nephropathy. Elevated levels of serum cholesterol, triglycerides and lipoproteins are the main lipid derangements in diabetes which are common risk factor for coronary artery disease. It is found that elevated blood glucose levels and duration of diabetes are responsible for nephropathy and microalbuminuria. However Apo B and Lp(a) increases in the microalbuminuria and macroalbuminuria respectively.

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