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Research Article

ASSESSMENT OF DYSLIPIDEMIA IN TYPE II DIABETES MELLITUS WITH SECONDARY COMPLICATIONS

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ABSTRACT

Objective: The main aim of the present study was to investigate the levels of lipid and lipoproteins in causing secondary microvascular complications in diabetic patients. Patients of Type II diabetes mellitus are highly susceptible to various complications due to long-term persistence of hyperglycemic state in the body. Thus, it is imperative to study the effect of hyperglycemia on lipids as their subsequent oxidation can lead to complications such as nephropathy, neuropathy, and retinopathy in diabetics which can further lead to macrovascular complications in the body.

Methods: The diabetic patients were divided into two groups, based on the presence/absence of secondary microvascular complications, namely, nephropathy, retinopathy, and neuropathy. Two types of cases were included in the study, on the basis of duration, namely, 0–5 years and 5–10 years duration. Blood samples were collected and levels of hemoglobin and glycated hemoglobin were determined. The biochemical parameters, namely, random blood sugar, cholesterol, triglycerides, high-density lipoproteins, low-density lipoproteins (LDLs), and very LDLs were estimated.

Results: The lipid levels altered in diabetic patients, leading to the dyslipidemia and the cumulative effect of hyperglycemia and dyslipidemia leads to the oxidative stress in the body. The increased oxidation of lipids may lead to the occurrence of microvascular complications in the body. Furthermore, dyslipidemia has been found more prevalent in males as compared to females.

Conclusion: Due to the increased prevalence of diabetes in India, funding of this study would suggest that there is a need to accelerate the importance of monitoring lipid levels in diabetes. Diabetic patients should routinely monitor their glycemic status, renal, and lipid profile to avert microvascular complications associated with diabetes mellitus.

Keywords: Diabetes mellitus, Microvascular complications, Dyslipidemia, Triglycerides, Hyperglycemia.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia (elevated levels of blood glucose), develops due to the defects in insulin secretion, insulin action, or both [1]. According to diabetes atlas, the global prevalence of diabetes is estimated at 415 million (8.8%) and predicted to rise to 642 million in the next 25 years. In India, there are about 70 million people with diabetes and are expected to cross 124 million by 2040 [2]. Chronicity of hyperglycemia is associated with long-term damage and failure of various organ systems mainly affecting the eyes, nerves, kidneys, and the heart [3]. Various disorders such as obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidemia lead to metabolic syndrome, responsible for the development of morbid and comorbid conditions [4]. The injurious effects of hyperglycemia are categorized into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy). Endothelial dysfunction is an early event involved in pathogenesis of vascular complications in Type II diabetes mellitus patients who have insulin resistance and usually relative (rather than absolute) insulin deficiency [5].

Diabetes induces oxidative stress in the body which could dearrange various metabolisms [6]. High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Moreover, this leads to the osmotic stress and it has been postulated as an underlying mechanism in the development of diabetic microvascular complications. These microvascular complications of diabetes depend on both the duration and the severity of hyperglycemia. High glucose concentrations can promote the non-enzymatic formation of advanced glycosylated end products [7]. The hyperglycemia promotes the formation of reactive oxygen species (ROS), which interacts with both deoxyribonucleic acid (DNA) and proteins, causing cellular damage, especially targeting mitochondrial DNA. A study on the human retinal endothelial cell demonstrated very early mitochondrial DNA damage with hyperglycemia-induced overproduction of ROS [8]. ROS-mediated cellular damage may be a form of pathologic "memory" in the microvasculature that persists even after glucose normalization.

The prevalence of diabetes has been increasing at an alarming rate, thus it is imperative to understand the relationship between diabetes and its secondary complications. Approximately 193 million diabetics in the world remain undiagnosed predisposing them to the development of several long-term complications of untreated chronic hyperglycemia. Although intensive glycemic control lowers the incidence and progression of microvascular complications, the morbidity associated with these complications is still increasing. Patients with microvascular complications appear particularly prone to accelerated atherosclerosis and premature death. The presence of microvascular disease is also a predictor of coronary heart events [9].

The Indians are more prone to diabetes whether they may be residing in India or outside due to the certain characteristics. Approximately 25% of the people with new detected diabetes already have microvascular disease, suggesting that they have had the disease for 4–7 years by the time of the diagnosis. Hence, in a patient with diabetes, it is important to consider the treatment of other conditions and complications when present, as they are likely to result in poor quality of life and adverse outcome.

METHODS

Type II diabetic patients who visit the outpatient departments of the Dr. Rohit Kapoor Clinic and Civil Hospital, Amritsar, and 30 healthy

Table 1: Description of subjects understudy

Total population (n=110)								
Healthy control (n=40)		**Diabetic patients without microvascular complications (n=40)**				**Diabetic patients with microvascular complications (n=40)**			
Females (n=20)	**Males (n=20)**	**Females (n=20)**		**Males (n=20)**		**Females (n=20)**		**Males (n=20)**	
-	-	0–5 (years)	5–10 (years)	0–5 (years)	5–10 (years)	0–5 (years)	5–10 (years)	0–5 (years)	5–10 (years)
-	-	n=10	n=10	n=10	n=10	n=10	n=10	n=10	n=10

Table 2: Mean age and weight of diabetic patients with or without microvascular complications

Group	**Duration of diabetes (years)**	**Number of patients (n)**	**Age (years)**	**Weight (kg)**	**Age**	**Weight**
			Females		**Males**	
Healthy controls (I)		20	45.52±13.9	65.66±9.36	54.1±12.17	74.3±2.79
Diabetic patients without	0–5	10	43.4±9.90	69±11.57	45.4±10.02	75.5±7.44
microvascular complications (II)	5–10	10	54.54±10.57	60.4±4.50	52.12±9.82	78.26±8.92
Diabetic patients with	0–5	10	57.5±6.20	71.45±8.84	54.9±10.39	75.25±11.44
microvascular complications (III)	5–10	10	60.3±10.13	65.31±10.61	58.9±8.24	78.84±10

*Data are represented as mean±standard deviation

Table 3: Hemoglobin and HbA_1C and diabetic patients with or without microvascular complications

Group	**Duration of diabetes (years)**	**Number of patients (n)**	**Hb (g/dl)**	**HbA_1C (g/dl)**	**Hb (g/dl)**	**HbA_1C (g/dl)**
			Females		**Males**	
Healthy control (I)		20	10.84±1.3	4.11±1.01	13.03±1.36	4.6±1.04
Diabetic patients without	0–5	10	10.8±1.11	7.17±0.90	12.37±1.07	8.16±1.31
microvascular complications (II)	5–10	10	10.30±0.96	7.65±0.90	11.86±0.98	7.23±1.19
Diabetic patients with	0–5	10	11.31±1.01	8.21±1.1	12.12±0.77	8.15±1.0
microvascular complications (III)	5–10	10	10.61±0.78	9.07±2.94	11.98±1.01	8.34±0.8

*Data are represented as mean±standard deviation. HbA_1C: Glycated hemoglobin, Hb: Hemoglobin

Table 4: RBS in diabetic patients with or without microvascular complications

Group	**Duration of diabetes (years)**	**Number of patients (n)**	**RBS (mg/dl)**	**RBS (mg/dl)**
Healthy control (I)		10	94.23±16.83	109.9±16.35
Diabetic patients without	0–5	10	94.23±16.83	223.3±25.89
microvascular complications (II)	5–10	10	204.4±37.43	216.25±33.30
Diabetic patients with	0–5	10	258.90±30.39	225.5±28.65
microvascular complications (III)	5–10	10	237.8±27.84	215.1±36.39

*Data are represented as mean±standard deviation. RBS: Random blood sugar

individuals, who came for routine checkup, considered as controls, were included in the study. The diabetic patients were divided into two groups, based on the presence/absence of secondary microvascular complications, namely, nephropathy, retinopathy, and neuropathy. Two types of cases were included in the study, on the basis of duration, namely, 0–5 years and 5–10 years duration (Table 1). This was confirmed by the patient's medical history procured from the hospital. Group-wise distribution of subjects understudy included Group 1: 30 healthy controls, Group 2: 40 diabetic subjects without microvascular complications, and Group 3: 40 diabetic subjects with microvascular complications. Inclusion criteria involve diabetic males and females, with or without complication, in the age frame of 30–70 years. Exclusion criteria included patients with hypothyroidism or hyperthyroidism, cardiac failure, renal failure, eye disorders before the onset of diabetes, and pregnant women. The study protocol was approved by the institutional ethical committee. Blood samples were collected from a prominent vein and level of hemoglobin (Hb) was estimated by Sahli's [10]. The biochemical parameters were estimated using beacon diagnostics and Erba diagnostic kits. The blood sugar level was estimated spectrophotometrically at 505 nm by glucose oxidase-peroxidase (POD) method [11]. Glycated Hb (HbA_1C) level was estimated by ion exchange resin method using a commercially available kit (ERBA Diagnostics Mannheim GmbH, Mannheim/Germany) [12]. The serum cholesterol level was estimated spectrophotometrically at 505 nm by cholesterol oxidase-POD aminophenazone (CHOD-PAP) method [13]. The serum triglyceride level was estimated spectrophotometrically at 505 nm by glycerol phosphate oxidase/POD method [14]. The serum high-density lipoproteins (HDLs) cholesterol level was estimated by CHOD-PAP after precipitating with phosphotungstic acid method. Very low-density lipoprotein (VLDL) cholesterol and LDL were calculated from Friedewald formula.

RESULTS AND DISCUSSION

The study included a total of 120 samples collected from healthy controls, diabetic patients with microvascular complications, and diabetic patients without microvascular complications. The blood samples were collected in aseptic conditions and renal profile, lipid profile, HbA_1C, random blood sugar, and hemoglobin were estimated in each patient.

The mean age of patients involved in the present study was 45–60 years. The weight of patients involved in the study was determined and was found comparative to each other (Table 2). The level of hemoglobin was

Table 5: Lipid profile of female diabetic patients with or without microvascular complications

Group	Duration of diabetes (years)	Cholesterol (mg/dl)	TG (mg/dl)	High-density lipoproteins (mg/dl)	Low-density lipoproteins (mg/dl)	Very low-density lipoproteins (mg/dl)
Healthy control (I)		142.85±22.15	132.61±23.97	45.33±12.82	73.32±23.13	26.60±4.76
Diabetic patients without microvascular complications (II)	0–5	151.4±20.83	163.4±25.14	40.6±2.12	77.4±17.51	32.68±3.43
	5–10	134.45±32.53	133±34.60	41.75±2.54	66.41±20.05	26.58±4.92
Diabetic patients with microvascular complications (III)	0–5	173.2±25.74	192±34.26	41.9±3.57	93.04±19.54	38.87±3.40
	5–10	139.4±32.17	153.2±32.49	40.9±2.23	65.11±20.76	33.79±2.63

*Data are represented as mean±standard deviation

Table 6: Lipid profile of male diabetic patients with or without microvascular complications

Group	Duration of diabetes (years)	Cholesterol (mg/dl)	TG (mg/dl)	High-density lipoproteins (mg/dl)	Low-density lipoproteins (mg/dl)	Very low-density lipoproteins (mg/dl)
Healthy control (I)		142.6±27.31	121.4±18.11	43.7±1.77	73.48±25.54	25.48±4.21
Diabetic patients without microvascular complication (II)	0–5	142.8±16.26	143.4±21.02	41±1.76	73.18±16.69	28.62±4.21
	5–10	164.37±18.21	153.75±35.63	38.25±4.13	97.5±15.51	30.75±3.13
Diabetic patients with microvascular complications (III)	0–5	161.2±28.39	188.1±32.58	39.9±3.54	83.68±16.84	37.68±4.1
	5–10	151±32	152±35.76	40±3.13	84.12±17.14	30.8±3.73

Data are represented as mean±standard deviation

found higher in male patients as compared to female patients but was lower as compared to healthy controls.

HbA_1C was found higher in diabetic patients as compared to controls (Table 3). Both male and female patients with microvascular complications had higher level of HbA_1C as compared to patients without microvascular complications with the increase in the duration of disease; HbA_1C levels have significantly increased, irrespective of gender differences. It can be inferred that the advanced glycation end products accumulated progressively in the tissues and organs. These products interfere with the normal functioning of organs and caused secondary complications of diabetes mellitus [15]. HbA_1C is a significant biochemical marker in the prediction of microvascular complications in diabetic patients. Several studies showed the significant elevation in the level of glycated hemoglobin in blood serum of diabetic patients [16]. HbA_1C also plays a significant role in the prediction of macrovascular complications as well [17].

In diabetic patients, hyperglycemic conditions arise due to non-utilization of glucose by body cells due to insulin resistance shown by the cells or due to insulin deficiency [18]. This can result in the abnormalities of carbohydrate, protein, and fat metabolism. Diabetic patients have poor glycemic control which ultimately increases the risk for secondary problems due to the persistent hyperglycemic condition in the body. In the present study, both male and female diabetic patients revealed higher level of random blood sugar irrespective of the presence or absence of complication (Table 4).

Diabetic patients with microvascular complications have high (173.2±25.74) level of cholesterol among all the studied groups. It has also been observed that cholesterol levels did not reveal any significant increase with the duration of disease. Females were found to have higher cholesterol levels as compared to male patients (Table 5).

Triglycerides also followed the same pattern. Healthy controls showed normal triglycerides levels in both the genders. However, the levels were higher in diabetic patients. Maximum triglyceride level was found to be 192.34±34.36 mg/dl and 188±32.58 mg/dl in female and male diabetic patients, respectively, with microvascular complications with 5 years of disease duration. HDL level did not show any significant differences among all the studied groups. Maximum level of HDL (45.33±12.82 mg/dl) and (43.7±1.77) was found in female and male healthy controls, respectively. LDL levels were higher in male diabetic patients with increased disease duration as compared to their female counterparts (Table 6). Insulin resistance leads to the increased susceptibility of LDL to oxidation, leading to impaired glucose tolerance. Increased LDL cholesterol could lead to its conversion to small dense LDL particles [19]. Higher level of LDL cholesterol found in males may be probably due to stressful life and high incidence of smoking in males. Estrogen protects against the risk factors of complications by decreased LDL cholesterol and lipoprotein. Estrogen also prevents the oxidation of LDL cholesterol. The levels of VLDL were found higher in female diabetic patients with microvascular complications, independent of the duration of disease.

Diabetic nephropathy and declining kidney function to be associated with high level of total cholesterol and triglyceride [20]. Studies have shown increased levels of total cholesterol and non-HDL cholesterol levels in diabetics and this was found to be associated with increasing severity of diabetic retinopathy [21]. Researchers have reported high levels of total cholesterol, HDL, and triglycerides in diabetic patients and other lipid abnormalities [18,22]. Abnormalities in lipid profile might be a result of unbalanced metabolic states of diabetic patients that include hyperglycemia and insulin resistance [23]. The variations of serum total lipid with sex are different which may be related to dietary habits and lifestyle [24]. Studies determined that serum triglycerides are more pronounced in females, either with insulin-dependent diabetes mellitus (IDDM) or with non-IDDM insulin treated-I than in male patients [13,25]. Differences in serum triglycerides may be related to a greater adverse effect of diabetes on triglyceride concentration in diabetic females than in diabetic males. This may explain the high risk of arteriosclerosis in diabetic females. Since, in normal subjects, serum triglyceride levels reveal higher values among males than in females, normal females usually have less arteriosclerosis vascular disease than in males as reported [26-28]. However, no significant difference was obtained in the level of serum cholesterol in diabetic and non-diabetic subjects in another study [29]. The increase of serum cholesterol level in diabetic patients may also be due to increased synthesis of cholesterol [30].

There is a clustering of interrelated plasma lipid and lipoprotein abnormalities, in diabetic patients and associated with increased risk of cardiovascular diseases. Insulin resistance altered metabolism of lipids and increased hepatic secretion of VLDL and its impaired clearance. Increased hepatic production or reduced clearance from plasma of large VLDL also results in increased production of precursors of small dense LDL patients. Insulin resistance plays a pivotal role in the development of diabetic dyslipidemia by influencing several factors.

Increased efflux of free fatty acids from adipose tissue and impaired insulin mediated skeletal muscle uptake of free fatty acids increased their flux to the liver [31].

Insulin resistance also increases hepatic lipase activity, which is responsible for hydrolysis of phospholipids in LDL and HDL particles and leads to smaller and denser LDL particles and decrease in HDL, and this ultimately leads to the emergence of complications in the body.

There are various factors which account for gender differences. There is a difference in pattern of obesity between males and females. High blood sugar levels damaged functional filtering units of kidneys and nephrons. As a result, kidneys are unable to maintain the fluid and electrolyte homeostasis. It has also been observed that with the advancement of age and duration of diabetes disease, renal parameters got altered, which indicated renal damage in diabetic patients. Renal disease in diabetes is found to be associated with abnormalities of vasodilatation and generated reactive oxygen species mediated by endothelial-derived nitric oxide, suggesting linkage between vascular and metabolic abnormalities. As the disease progresses, albumin leaks into urine and filtering function of kidney begins to drop, resulting in body's retention of various wastes [32].

CONCLUSION

It was concluded that the lipid parameters get altered in diabetic patients, leading to the dyslipidemia. The cumulative effect of hyperglycemia and dyslipidemia leads to the oxidative stress in the body. The increased oxidation of lipids may lead to the occurrence of microvascular complications in the body. Due to the increased prevalence of diabetes in India, funding of this study would suggest that there is a need to accelerate the importance of monitoring lipid levels in diabetes. Diabetic patients should routinely monitor their glycemic status, renal, and lipid profile to avert microvascular complications associated with diabetes mellitus.

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