THE EXPERIMENT
INTERNATIONAL JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN-2319-2119

RESEARCH ARTICLE

Siva.L et al, **The** *Experiment, 2013 Vol. 16(2), 1112-1122*

PREDICTOR OF CORONARY HEART DISEASE IN DIABETICS

ABSTRACT

Diabetes mellitus is associated with a high risk of cardiovascular disease (CVD). The management of diabetic dyslipidemia, a well-recognized and modifiable risk factor, is a key element in the multifactorial approach to prevent CVD in individuals with type 1 and type 2 diabetes. Type 1 and Type 2 diabetes are associated with marked increased risk of cardiovascular disease (CVD). A greater burden of risk factors is at least partly responsible for the increased risk of CHD in diabetes. Dyslipidemia is a well-recognized and modifiable risk factor that should be identified early to institute aggressive cardiovascular preventive management.

KeyWords Coronary heart disease(CHD), HDL-Cholesterol, LDL-Cholesterol, VLDL-Cholesterol, Lipoprotein lipase(LPL),Cardio Vascular Disease(CVD), Glycosylated haemoglobin(HbA1c),SLIMS(Sri Lakshminarayana Institute of Medical Sciences, Puducherry).

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by uncontrolled blood glucose levels. The prevalence of diabetes mellitus in World population is increasing in epidemic. The increasing prevalence of diabetes merits concern because the disease puts those afflicted at risk for vascular and nervous systems[1] (Gerich, 2001). Between 1980 and 2003, the prevalence of diabetes is more than doubled, rising from 5.8 to 13.8 million diagnosed individuals. Indeed, throughout the world the number of people with diabetes is projected to increase from 285 million in 2010 to 439 million in 2030[2] (Wild et al., 2004). Individuals with diabetes have an absolute risk of major coronary events similar to that of nondiabetic individuals with established coronary heart disease (CHD)[3] (Haffner et al.,1998). Early, aggressive pharmacological management is advocated to reduce low-density lipoprotein cholesterol levels, regardless of baseline levels.

MATERIAL & METHODS

Eighty five patients each of type I and type II diabetes of not more than 3 years duration were selected for the study. Eighty five individuals with no diabetes and absence of any systemic illness comprises the control group. Samples were collected from diabetic patients and normal individuals as per the guidelines of ICMR, New Delhi, India. Informed written consent was obtained from all subjects after explanation of the nature, purpose and potential risks of the study. History of presenting complaints was obtained from each patient. The case history of the patients was obtained using a standard data collection sheet. The routine biochemical parameters like plasma glucose(GOD-POD Method), HbA1c(Ion-Exchange resin method), Cholesterol(CHOD-PAP Method), Triglycerides(GPO-PAP Method), HDL-Cholesterol(GPO-PAP Method), were analysed at the clinical biochemistry laboratory of SLIMS. (LDL-Cholesterol and VLDL-Cholesterol was calculated using Friedwald's equation).

Exclusion criteria

Other endocrinological dysfunctions, infectious diseases, malignancy, any other systemic illness, patients with history of cerebrovascular event or myocardial infarction, patients with a serum creatinine more than 1.5 mg/dl. Those who received antihypertensive and/or diuretic drugs within the last one month will not be included in the study.

Chemicals

All the chemicals were purchased from National scientific suppliers, Puducherry, all of them were analytical grade.

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STATISTICS

Results will be expressed as mean ± SD. Multiple comparisons of the significant ANOVA will be performed by Duncan's multiple comparison test. A P-value <0.001 was considered as statistically significant. All data will be analyzed with the aid of statistical package program SPSS 10.0 for Windows.

RESULTS AND DISCUSSIONS

Blood glucose and HbA1c

Normally, diabetes is detected by measuring fasting plasma glucose blood levels. However, due to wide deviations in the circulating glucose concentrations, a randomized glucose measurement does not provide clear data for overall glycemic control. A better method to evaluate the level of control is the measurement of the HbA1c value, which is a normally used laboratory test for measuring long-term diabetic control[4] (Andrade-Cetto et al., 2008). In addition, diabetic patients have reduced glucose tolerance. Figure 1 & 2 shows the levels of blood glucose and HbA1c of normal and diabetic subjects.

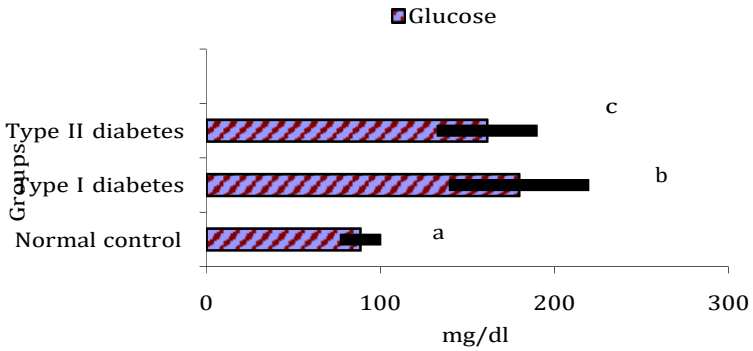

Figure .1. Level of plasma glucose in normal control and type I & type II diabetic patients

Results are mean±SD for 85 samples. Values are expressed as mg/dl. Values that have a different superscript (a,b,c) differ significantly with each other (P<0.05). Duncan's Multiple Range Test.

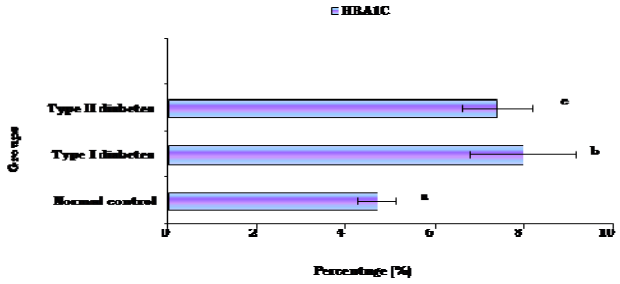

Figure .2. Level of HBA1C in normal control and type I & type II diabetic patients

Results are mean±SD for 85 samples. Values are expressed as mg/dl. Values that have a different superscript (a,b,c) differ significantly with each other (P<0.001). Duncan's Multiple Range Test.

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Variables	**Controls (n=85)**	**Type I (n=85)**	**Type II (n=85)**	**Significant values**		
				Controls-Type I	**Controls-Type II**	**Type 1 vs Type 11**
Glucose (mg/dl)	88.58±11.14	179.66±39.64	161.34±28.26	<0.001**	<0.001**	<0.001**

Table .1. Levels of fasting plasma glucose in control, Type I DM & in Type II DM

Results are presented in Mean ± S.D. P values are obtained by ANOVA with Post-hoc test.
**-Strongly significant.

Variables	**Controls (n=85)**	**Type I (n=85)**	**Type II (n=85)**	**Significant values**		
				Controls-Type I	**Controls-Type II**	**Type 1 vs Type 11**
HbA_1c(%) c(%)	4.68±0.43	7.96±1.20	7.38±0.79	<0.001**	<0.001**	<0.001**

Table .2. Levels of HbA1c in control, Type I DM & in Type II DM
Results are presented in Mean ± S.D. P values are obtained by ANOVA with Post-hoc test.
**-Strongly significant.

From the results obtained, it was evident that fasting plasma glucose levels and Hb1Ac values were intensely raised in Type I and Type II diabetic patients. In the present study as shown in the table **.1**, there is a significant increase in the levels of fasting blood glucose in type 1 DM subjects(mean ±sd,179.66±39.64) compared to control healthy subjects(mean±sd,88.58±11.14) at p<0.001. As shown in the table .1.,there is significant increase in the levels of fasting blood glucose in type 2 DM subjects(mean±sd,161.34±28.26) compared to control healthy subjects (mean±sd, 88.58±11.14) at p<0.001. Also, significant increase in the levels of fasting blood glucose in type 1 DM subjects(mean ±sd,179.66±39.64) compared to type 2 DM subjects(mean±sd,161.34±28.26) at p<0.001. In the present study as shown in the table .**2**., there is a significant increase in the levels of HbA1c in type 1 DM subjects(mean ±sd,7.96±1.20) compared to control healthy subjects(mean±sd,4.68±0.43) at p<0.001.There is significant increase in the levels HbA1c of in type 2 DM subjects(mean±sd,7.38±0.79) compared to control healthy subjects (mean±sd, 4.68±0.43) at p<0.001. Also, significant increase in the levels of HbA1c in type 1 DM subjects(mean ±sd,7.96±1.20) compared to type 2 DM subjects(mean±sd, 7.38±0.79) at p<0.001.

In uncontrolled or poorly controlled diabetes, there is an increased glycation of a number of proteins including hemoglobin and α-crystalline of lens[5] (Pasupathi et al., 2008). Glycated hemoglobin (HbA1c) was found to increase in patients with diabetes mellitus and the amount of increase is directly proportional to the fasting blood glucose level[6] (Koenig et al., 1976). The level of glycated hemoglobin is measured as one of the markers of degree of oxidative stress in diabetes mellitus.

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Persistent hyperglycemia results in glycation of Hb and that leads to the formation of HbA1c[7] (Yabe-Nishimura, 1998). The noted increase in the levels of HbA1c in Type I diabetics implies the oxidation of sugars, extensive damage to both sugars and proteins in the circulation, vascular wall and lens proteins thereby continuing and reinforcing the cycle of oxidative stress and damage. This concurs with an earlier reported study[8] (Huebschmann et al., 2006). Agents with antioxidant or free radical scavenging power have been reported to inhibit oxidative reactions associated with glycation[9] (Elgawish et al., 1996).

Cholesterol and Triglycerides

Diabetes mellitus, an endocrine disorder, is a major source of morbidity in developed countries. The metabolism of all fuels including carbohydrates, fats and proteins are altered in diabetes and patients with diabetes have lipid disorders and an increased risk of coronary heart disease, peripheral vascular disease and cerebrovascular disease[10] (Asakawa et al., 2000). Diabetes is associated with profound alterations in the plasma lipid and lipoprotein profile [as observed in the present study **(**Figure.3-8)] and with an increased risk of premature atherosclerosis, coronary insufficiency and myocardial infarction[11] (Reasner et al., 2008). Accumulation of lipids in diabetes is mediated through a variety of derangements in metabolic and regulatory processes, especially insulin deficiency, thereby rendering the diabetic patient more prone to hypercholesterolemia and hypertriglyceridemia[12] (Jaiprakash et al., 1993).

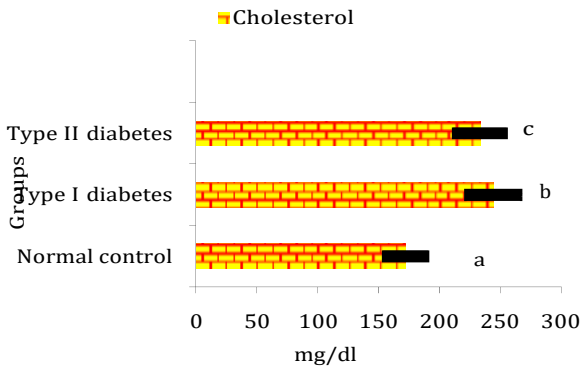

Figure .3. Level of cholesterol in normal control and type I & type II diabetic patients

Results are mean±SD for 85 samples. Values are expressed as mg/dl. Values that have a different superscript (a,b,c) differ significantly with each other ($P<0.05$). Duncan's Multiple Range Test.

One of the major pathogenesis of lipid metabolism disturbances in diabetes is the increased mobilization of fatty acids from adipose tissue and secondary elevation of free fatty acid level in the blood[13] (Shanmugam et al., 2009). Excessive lipolysis has been found to occur during diabetes. One of the consequences of excessive mobilization of fatty acid is the production of ketone bodies in the liver. The excessive lipolysis in diabetics leads to increase free fatty acids in circulation. They enter the liver and are esterified to form triglycerides. Fatty acids are required for both the structure and function of every cell in the body and they form an important component of cell membranes. Several authors have reported that, the fatty acid compositions of various tissues are altered in both experimental and human diabetes[14,15] (Xinhua Chen et al., 2010; Xianlin Han et al., 2010). Hence, it is postulated that circulatory lipids may play an imperative role in progression of diabetes, not only by way of hyperlipidemia and the development of atherosclerosis leading to myocardial infarction, but also by modifying the composition, structure and firmness of cellular membranes.

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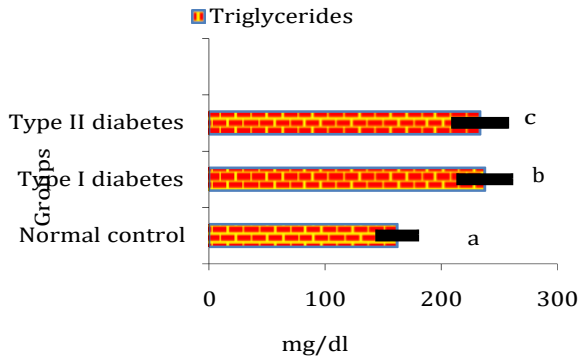

Figure .4. Level of triglycerides in normal control and type I & type II diabetic patients

Results are mean±SD for 85 samples. Values are expressed as mg/dl. Values that have a different superscript (a,b,c) differ significantly with each other (P<0.001). Duncan's Multiple Range Test

Variables	**Controls (n=85)**	**Type I (n=85)**	**Type II (n=85)**	**Significant values**		
				Controls-Type I	**Controls-Type II**	**Type 1 vs Type 11**
Total cholesterol (mg/dl)	172.00±18.34	243.96±22.83	232.98±21.93	<0.001**	<0.001**	0.002**

Table .3. Levels of Total cholesterol in control, Type I DM & in Type II DM

Results are presented in Mean ± S.D. P values are obtained by ANOVA with Post-hoc test.
**-Strongly significant.

Variables	**Controls (n=85)**	**Type I (n=85)**	**Type II (n=85)**	**Significant values**		
				Controls-Type I	**Controls-Type II**	**Type 1 vs Type 11**
Triglycerides (mg/dl)	162.08±17.82	237.46±23.49	233.45±23.89	<0.001**	<0.001**	0.458

Table . 4. Levels of triglycerides in control, Type I DM & in Type II DM

Results are presented in Mean ± S.D. P values are obtained by ANOVA with Post-hoc test.
**-Strongly significant

Hypercholesterolemia, high concentration of low-density lipoprotein cholesterol, hypertriglyceridemia and low high-density lipoprotein are established as independent risk factors for diabetes[16] (Smith et al., 2007). The pathogenesis is multifactorial, reflecting complex biosynthetic, enzymatic and catabolic derangement in lipoprotein metabolism. Alterations in the fatty acid composition of serum triglycerides, cholesterol ester and phospholipids were also reported in diabetes condition[17] (Vijayaraghavan, 2010). In the present study

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as shown in the table.3&4 ,there is a significant elevation in the levels of total cholesterol and triglycerides was observed in Type I and Type II diabetic patients as compared to normal healthy individuals (Figure .3&4). In the present study as shown in the table.3 **,** there is a significant increase in the levels of total cholesterol in type 1 DM subjects(mean ±sd, 243.96±22.83) compared to control healthy subjects(mean±sd, 172.00±18.34) at p<0.001.There is significant increase in the levels of total cholesterol in type 2 DM subjects(mean±sd, 232.98±21.93) compared to control healthy subjects (mean±sd, 172.00±18.34) at p<0.001. Also,there is no significant increase in the levels of total cholesterol in type 1 DM subjects(mean ±sd, 243.96±22.83) compared to type 2 DM subjects(mean±sd, 232.98±21.93) at p<0.002. In the present study as shown in the table .**4.,** there is a significant increase in the levels of triglycerides in type 1 DM subjects(mean ±sd, 237.46±23.49) compared to control healthy subjects(mean±sd, 162.08±17.82) at p<0.001.There is significant increase in the levels of triglycerides in type 2 DM subjects(mean±sd, 233.45±23.89) compared to control healthy subjects (mean±sd, 162.08±17.82) at p<0.001. Also,there is no significant increase in the levels of triglycerides in type 1 DM subjects(mean ±sd, 237.46±23.49) compared to type 2 DM subjects(mean±sd, 233.45±23.89) at p<0.458.Interestingly, a slightly higher elevation in these parameters was recorded in Type II diabetic patients as compared to Type I diabetic patients. The levels of VLDL and LDL cholesterol were significantly higher in Type I and Type II diabetic subjects, while a concomitant decline was noted in HDL cholesterol level (Figure.5-7). In the present study, as shown in the table.5. ,there is a significant increase in the levels of VLDL-cholesterol in type 1 DM subjects(mean ±sd, 47.27±4.58) compared to control healthy subjects(mean±sd, 32.60±3.45) at p<0.001.There is significant increase in the levels of VLDL-cholesterol in type 2 DM subjects(mean±sd, 46.45±4.70) compared to control healthy subjects (mean±sd, 32.60±3.45) at p<0.001. Also, there is no significant increase in the levels of VLDL-cholesterol in type 1 DM subjects(mean ±sd, 47.27±4.58) compared to type 2 DM subjects(mean±sd, 46.45±4.70) at p<0.422.

Studies by Jaiprakash et al.[12] (1993) have shown that diabetes mellitus enhances the deposition of lipids through a multiple derangements in catabolic and anabolic processes, considering the diabetic patient more susceptible to atherosclerosis. The major pathogenesis of lipid metabolism disturbances in diabetes is the enhanced mobilization of free fatty acids from adipose tissue and secondary elevation of free fatty acid level in the blood[18] (Adilson Guilherme et al., 2008), as observed in the present study.

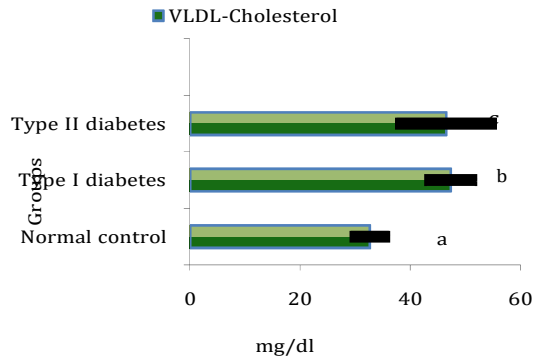

Figure.5. Level of VLDL-cholesterol in normal control and type I & type II diabetic patients

Results are mean±SD for 85 samples. Values are expressed as mg/dl. Values that have a different superscript (a,b,c) differ significantly with each other (P<0.001). Duncan's Multiple Range Test.

Diabetes is characterized by hyperglycemia together with biochemical aberrations of glucose and lipid metabolism. The objectives of managing diabetes mellitus are to optimize the control of blood glucose, diminish the adverse effects of oxidative stress, and normalize instabilities in lipid metabolism. Marked increase noticed in the lipid content of serum in diabetes is mainly due to the increased mobilization of free fatty acids from peripheral deposits[19](Al- Shamaony et al., 1994).

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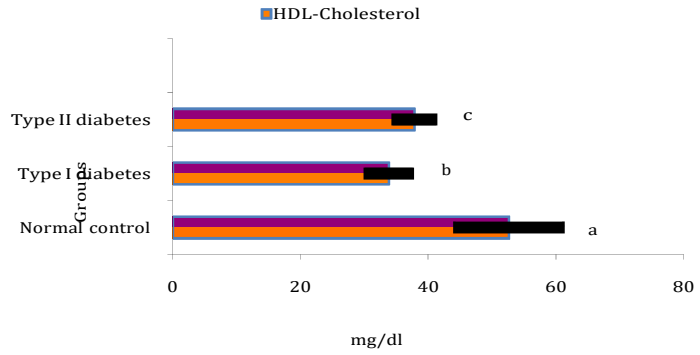

Figure.6. Level of HDL-cholesterol in normal control and type I & type II diabetic patients

Results are mean±SD for 85 samples. Values are expressed as mg/dl. Values that have a different superscript (a,b,c) differ significantly with each other (P<0.001). Duncan's Multiple Range Test.

On the other hand, glucagon, catecholamines and other hormones enhance lipolysis[20] (Marcus et al., 1988). The noticeable hyperlipidemia that exemplifies the diabetic state may therefore be regarded as a magnitude of the uninhibited actions of lipolytic hormones on the fat depots. Diabetes is also known to be associated with an increase in the synthesis of cholesterol, which may be due to the increased activity of HMG CoA reductase[21] (Jingming Li et al., 2009). A previous report indicate that plasma HDL cholesterol is low in untreated insulin-deficient diabetics[22] (Chen et al., 1987), as observed in the present observation, which was associated with a decline in HDL-turnover rate. In the present study,as shown in the table .6, there is a significant decrease in the levels of HDL-Cholesterol in type 1 DM subjects(mean ±sd, 33.84±3.74) compared to control healthy subjects(mean±sd, 52.60±8.54) at p<0.001.There is significant decrease in the levels of HDL-Cholesterol in type 2 DM subjects(mean±sd, 37.82±3.43) compared to control healthy subjects (mean±sd, 52.60±8.54) at p<0.001. Also, slightly a significant decrease in the levels of HDL-Cholesterol in type 1 DM subjects(mean±sd, 33.84±3.74) compared to type 2 DM subjects(mean ±sd, 37.82±3.43) at <0.001.

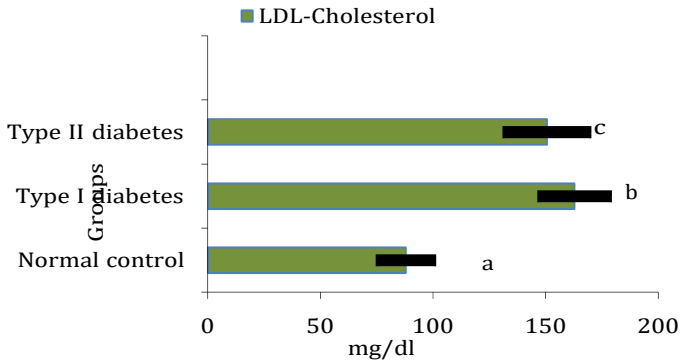

Figure .7. Level of LDL-cholesterol in normal control and type I & type II diabetic patients

Results are mean±SD for 85 samples. Values are expressed as mg/dl. Values that have a different superscript (a,b,c) differ significantly with each other (P<0.001). Duncan's Multiple Range Test.

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Studies by Simsolo et al.[23] (1992) have shown that the HDL-cholesterol levels correlate with lipoprotein lipase (LPL) levels in type II diabetes patients. It is demonstrated that VLDL and chylomicrons contribute surface apoproteins and lipids to HDL during hydrolysis by LPL. Investigations by Lopes-Virella et al.[24] (1983) have suggested that increased LDL-cholesterol may arise from glycosylation of the lysyl residues of apoprotein B as well as from decreasing affinity for the LDL receptor. The ability of LDL-cholesterol to form free radical mediated deterioration was found specifically responsible for the atherogenesis in diabetic patients[25] (Kondo et al., 2001). In the present study as shown in the table.7. , there is a significant increase in the levels of LDL-Cholesterol in type 1 DM subjects(mean ±sd, 162.82±15.96) compared to control healthy subjects(mean±sd, 87.96±12.82) at p<0.001.There is significant increase in the levels of LDL-Cholesterol in type 2 DM subjects(mean±sd, 150.55±19.2) compared to control healthy subjects (mean±sd, 87.96±12.82) at p<0.001. Also,there is significant increase in the levels of LDL-Cholesterol in type 1 DM subjects(mean ±sd, 162.82±15.96) compared to type 2 DM subjects(mean±sd, 150.55±19.2) at p<0.001.

Variables	**Controls (n=85)**	**Type I (n=85)**	**Type II (n=85)**	**Significant values**		
				Controls-Type I	**Controls-Type II**	**Type 1 vs Type 11**
VLDL(mg/dl)	32.60±3.45	47.27±4.58	46.45±4.70	<0.001**	<0.001**	0.422

Table .5. Levels of VLDL-Cholesterol in control, Type I DM & in Type II DM
Results are presented in Mean ± S.D. P values are obtained by ANOVA with Post-hoc test.
**-Strongly significant.

Variables	**Controls (n=85)**	**Type I (n=85)**	**Type II (n=85)**	**Significant values**		
				Controls-Type I	**Controls-Type II**	**Type 1 vs Type 11**
HDL (mg/dl)	52.60±8.54	33.84±3.74	37.82±3.43	<0.001**	<0.001**	<0.001**

Table .6. Levels of HDL-Cholesterol in control, Type I DM & in Type II DM
Results are presented in Mean ± S.D. P values are obtained by ANOVA with Post-hoc test.
**-Strongly significant

Variables	**Controls (n=85)**	**Type I (n=85)**	**Type II (n=85)**	**Significant values**		
				Controls-Type I	**Controls-Type II**	**Type 1 vs Type 11**
LDL (mg/dl)	87.96±12.82	162.82±15.96	150.55±19.2	<0.001**	<0.001**	<0.001**

Table .7. Levels of LDL-Cholesterol in control, Type I DM & in Type II DM

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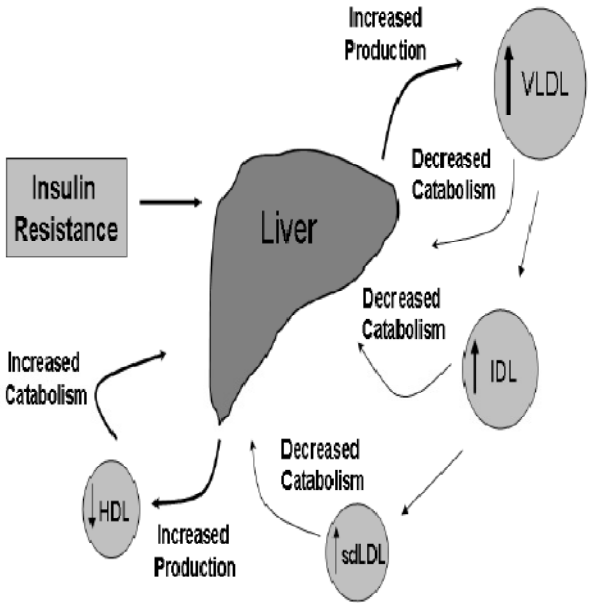

Figure .8. Dyslipidemia and alterations in lipoprotein metabolism associated with diabetes mellitus.
{Arterioscler Thromb Vasc Biol 28(7): 1225-1236 (2008)}

Insulin resistance is a multisystem disorder that induces multiple metabolic alterations. Factors that contribute to insulin resistance are genetics, obesity, physical inactivity, and advancing age[26] (Grundy et al., 1999). Patients with insulin resistance often have abdominal obesity[27] (Abate et al., 1995). Metabolic risk factors that occur commonly in patients with insulin resistance are atherogenic dyslipidemia, hypertension, glucose intolerance, and a prothrombotic state[28] (Reaven et al., 1996). Significant ($p<0.001$) elevation noticed in the levels of cholesterol and triglycerides in serum of Type I and Type II diabetic patients, which is an indication of severity of diabetes. This concurs with an earlier reported clinical study[29] (Fox and Muntner, 2008), which have shown that high level of circulating cholesterol and its accumulation in the tissues are well associated with diabetes. The level of LDL cholesterol was significantly ($p<0.001$) higher in Type I and Type II diabetes, whereas HDL cholesterol levels were significantly lower compared to normal healthy individuals. Hypertriglyceridemia is a common finding in patients with diabetes mellitus and is responsible for vascular complications[30] (Kudchodkar et al., 1988). Braun and Severson[31] (1992) have reported that deficiency of lipoprotein lipase (LPL) activity may contribute significantly to the elevation of triglycerides in diabetes. Lopes-Virella et al.[24] (1983) reported that treatment of diabetes with insulin served to lower plasma triglyceride levels by returning lipoprotein lipase levels to normal. Lipoprotein metabolism plays a pivotal role in diabetes, leading to vascular damage[26] (Grundy et al., 1999).

CONCLUSION

It is observed from the above study that the increased levels of HbA1c indicates there is uncontrolled diabetes. The levels of total cholesterol and triglycerides is found to be increased in diabetics. The levels of HDL-Cholesterol is found to be decreased which predicts

that the diabetics are more vulnerable to coronary heart disease as is the finding evidenced by increased levels of LDL-Cholesterol. Hence, there is a chance for predicting cardiovascular disease in diabetics, if detected early. Type 1 and type 2 diabetes is associated with a characteristic atherogenic lipid pattern of elevated serum cholesterol, triglycerides, low serum HDL-C levels, and a preponderance of small, dense LDL particles. Disturbance of lipid metabolism linked to insulin resistance may be the primary event in the development of type 2 diabetes. In order to reduce the risk of CVD in patients with type 1 and type 2 diabetes, physicians must initiate early and effective lipid-lowering therapy. Although the first priority of treatment is to lower LDL-C in patients with type 1 and type 2 diabetes, the atherogenic pattern of dyslipidemia associated with type 1 and type 2 diabetes may require an advanced treatment approach that ultimately aims for full normalization of the lipid profile to decrease cardiovascular risk.

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