Role of Glycemic control and Lipid profiles in management of Diabetic complications

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Abstract

Background & Objectives: Diabetes mellitus is one of the most common endocrine disorders affecting about 6% of the world's population. Diabetes mellitus is the leading cause of end stage renal disease (ESRD), a major cause of non-traumatic amputations, responsible for preventable blindness and a leading cause of cardiovascular mortality.
Hyperglycemia and dyslipidemia play an important role in the development of microvascular and macrovascular complications, leading to significant impact on the quality of life.

The objective of the study was to assess the glycemic control by estimation of glycosylated hemoglobin (HbA_{1c}), and lipid profile in patients of Diabetes mellitus without complications and in Diabetes mellitus with complications like neuropathy, retinopathy and nephropathy and compare with controls.

Methods: The present study comprised of 100 clinically diagnosed and confirmed cases of type 2 Diabetes mellitus attending and admitted in Navodaya Medical College Hospital and Research centre, Raichur.
The subjects were grouped as follows
Age and Sex matched controls - 25
Group A. Diabetes mellitus without complications - 25
Group B. Diabetes mellitus with retinopathy - 25
Group C. Diabetes mellitus with nephropathy - 25
Group D. Diabetes mellitus with peripheral neuropathy - 25

Glycosylated hemoglobin (HbA_{1c}), Total Cholesterol, Triglycerides and HDL-Cholesterol were estimated in all groups. LDL-Cholesterol and VLDL-Cholesterol were calculated in all groups by using Friedewald's formula.

Results: Our study showed that HbA_{1c} levels were significantly higher ($p<0.01$) in all groups of patients as compared to controls. The increase in Serum Cholesterol, Triglyceride, LDL-Cholesterol, VLDL-Cholesterol and decrease in HDL-Cholesterol levels were statistically significant ($p<0.01$) in Diabetic retinopathy group and Diabetic nephropathy group as compared to controls, whereas in Diabetic neuropathy group and in Diabetes mellitus without complication, the increase in Serum Cholesterol, Triglyceride, LDL-Cholesterol, VLDL-Cholesterol and decrease in HDL-Cholesterol levels was not statistically significant as compared to controls.

Conclusion: Impaired insulin secretion or insulin resistance impairs glucose utilization by the insulin sensitive tissue which in turn increases hepatic output of glucose, contributing to hyperglycemia. Hyperglycemia leads to diverse cellular and organ dysfunction. Dyslipidemia acts synergistically with hyperglycemia in the development of Diabetes mellitus associated complications.

Our study revealed that poor glycemic control and dyslipidemia are associated with Diabetic complications like neuropathy, retinopathy and nephropathy. Estimation of glycosylated hemoglobin and lipid profile helps in predicting the development of microvascular complications. Therefore intensive glycemic control and aggressive treatment of dyslipidemia can help in reducing Diabetes mellitus associated complications.

Key words: Hyperglycemia; glycosylated hemoglobin; dyslipidemia; end stage renal disease (ESRD); retinopathy; lipid profile; neuropathy.

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Introduction

Diabetes mellitus is a chronic devastating metabolic disorder virtually affecting every organ in the human system. The World today is witnessing an epidemic of Diabetes mellitus. Globally and nationally, Diabetes mellitus and its complications has become the most important contemporary and challenging health problem. Diabetes mellitus is associated with the highest co-morbidities and complications as compared to any other non-communicable disease.

Current estimates show that there are 171 million people suffering from Diabetes mellitus worldwide[1]. Two thirds of this population resides in developing countries. A recent estimate suggested that Diabetes mellitus was the fifth leading cause of death worldwide and was responsible for almost 3 million deaths annually (1.7–5.2% of deaths worldwide).[2] The explosion in the number of people with Diabetes

mellitus is due to ageing, urbanization, increasing prevalence of obesity and sedentary life style.

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion and / or insulin action. This results in hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. The metabolic dysregulation associated with Diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual.

The long-term effects of Diabetes mellitus include progressive development of the specific complications to the vital organs of the body. It may lead to retinopathy with potential blindness, nephropathy that may lead to renal failure, neuropathy with risk of foot ulcers leading to amputation and features of autonomic dysfunction. People with Diabetes mellitus are at increased risk of cardiovascular disease, peripheral vascular disease and cerebrovascular disease.

Hyperglycemia contributes significantly to the development of microvascular and macrovascular complications. Intensive glycemic control will delay the development or slow the progression of complications. This ensures a better quality of life for the patient. Glycosylated hemoglobin is an accurate and reliable test for assessing glycemia. The glycosylated hemoglobin reflects overall blood glucose levels over a period of two to three months.

In this study we estimated the glycosylated hemoglobin in patients of Diabetes mellitus without complications and with complications like retinopathy, nephropathy and neuropathy.

Dyslipidemia has a strong association with increased risk of macrovascular and microvascular complications. Hence in this study we assessed the Serum Cholesterol, Serum Triglycerides, High density lipoproteins (HDL), Low density lipoproteins (LDL), and Very low density lipoproteins (VLDL) in Diabetes mellitus patients without complications and with complications like retinopathy, nephropathy and neuropathy.

Materials and Methods

- Present study comprises of 100 confirmed cases of Type 2 Diabetes mellitus with and without complications, attending and admitted in Navodaya Medical College Hospital and Research center, Raichur.
- The age of the patients ranged from 45-65 yrs of both sexes.
- The study was conducted from February 2010 to January 2011.
- Informed consent was taken from controls and cases before collecting the blood sample.
- The study was approved by the ethical committee of the college. The controls and patients participated voluntarily in the study.

The present study comprised of 125 subjects.

Age and Sex matched controls - 25

Group A. Diabetes Mellitus without complications - 25

Group B. Diabetes Mellitus with retinopathy - 25

Group C. Diabetes Mellitus with nephropathy - 25

Group D. Diabetes Mellitus with peripheral neuropathy - 25

Selection criteria for the patient:

Inclusion criteria:

1. Clinically diagnosed and confirmed cases of type 2 Diabetes mellitus
2. Type 2 Diabetes mellitus with complications like retinopathy, nephropathy, and peripheral neuritis.

Exclusion criteria:

1. Chronic alcoholics
2. Smokers.
3. Juvenile diabetes.
4. Gestational diabetes.

Statistical analysis: Done by using One-way analysis of variance (ANOVA)

Collection of blood sample

Blood samples were collected in fasting conditions under aseptic conditions. 6ml of blood was collected from the cubital vein. Out of this 1ml was collected in EDTA bulb for estimation of glycosylated hemoglobin. Remaining sample was allowed to clot and serum was separated by centrifugation. The following parameters were estimated.

- Blood glucose
- Glycosylated hemoglobin and
- Lipid profile

Lipid profile comprised of - Serum cholesterol
- Serum triglyceride
- High density lipoproteins
- Very low density lipoproteins
- Low density lipoproteins

Methods

1) **Estimation of Blood Glucose Method:** GOD-POD: (Glucose oxidase –Peroxidase) end point colorimetric method.[13]

Using kit by Span diagnostics limited.

2) **Estimation of Glycosylated Haemoglobin Method:** Cation ion exchange method. [14]

Using glycosylated hemoglobin kit by Accurex Biomedical Pvt. Ltd.

3) **Estimation of Serum Cholesterol Method: CHOD-PAP (cholesterol oxidase – phenol aminophenozone) method.[15]**

Using kit by Span diagnostics limited

4) **Estimation of Serum Triglycerides Method: GPO(glycerol phosphate oxidase)- Trinder method.[16]**

Using kit by Transasia bio-medicals

5) **Estimation of HDL-Cholesterol Method: CHOD-PAP (cholesterol oxidase – phenol aminophenozone) method.[15]**

Using kit from Span diagnostics

6) **Calculation of LDL cholesterol and VLDL-cholesterol By using Friedewald's equation[15]**

- LDL-C = Total Cholesterol _ $\frac{\text{Triglycerides}}{5}$ _ HDL-C

Normal value = 50- 150 mg/dl.

Friedewald calculation is unsuitable when triglyceride level is more than 400 mg/dl.

- VLDL-C = $\frac{\text{Triglycerides}}{5}$

Results

Statistical analysis was done by One-way analysis of variance (ANOVA), followed by Dunnett multiple comparison post hoc tests. Pearson's correlation was applied to correlate between the parameters. . Significance of correlation was decided based on Pearson's correlation coefficient 'r' & 'p' values. A $p<0.05$ was considered to be statistically significant and <0.01 considered to be statistically highly significant. Statistical analysis was performed by using Minitab 14.0. The results were expressed as mean±standard deviation (SD).

Table 1: Age and sex distribution in each group

Characteristic	Controls	Cases			
		DM without complications	DM with Neuropathy	DM with Retinopathy	DM with Nephropathy
Age(years)	56.80±5.74	54.80±5.82	58.76±4.80	58.44±5.02	62.08±3.97
Male	19	16	18	13	19
Female	6	9	7	12	6

Prevalence of diabetes increases with age and complications of diabetes are also found in advanced age group.

Table 2: Fasting Blood Glucose levels in controls, Diabetes mellitus without complications, Diabetic neuropathy, Diabetic retinopathy and Diabetic nephropathy

	Controls (mg/dl)	Cases			
		DM without complications (mg/dl) (A)	DM with Neuropathy (mg/dl) (B)	DM with Retinopathy (mg/dl) (C)	DM with Nephropathy (mg/dl) (D)
FBS	99.02±10.74	140.63±29.86	180.11±24.88	227.84±34.50	262.84±24.24
p value		<0.01	<0.01	<0.01	<0.01

FBS found significantly high in DM with complications.

There was statistically significant increase ($p<0.01$) in the fasting blood glucose level in all groups as compared to controls.

Table 3: HbA_{1c} levels in controls, Diabetes mellitus without complications, Diabetic neuropathy, Diabetic retinopathy and Diabetic nephropathy

	Controls (%)	Cases			
		DM without complications(%) (A)	DM with Neuropathy(%) (B)	DM with Retinopathy(%) (C)	DM with Nephropathy(%) (D)
HbA_{1c}	5.55±0.50	7.51±1.32	10.12±1.28	12.29±1.28	14.29±1.08
p value		<0.01	<0.01	<0.01	<0.01

High level of glycated hemoglobin found in DM with complications.

The increase in the HbA_{1c} levels in all groups studied was statistically significant ($p<0.01$) as compared to controls.

Table 4: Lipid profile in controls, Diabetes mellitus without complications, Diabetic neuropathy, Diabetic retinopathy and Diabetic nephropathy

Parameter	Controls (mg/dl)	Cases			
		DM_without complications (mg/dl) (A)	DM with Neuropathy (mg/dl) (B)	DM with Retinopathy (mg/dl) (C)	DM with Nephropathy (mg/dl) (D)
Cholesterol	262.58±29.19	283.71±21.44	278.78±27.43	299.85±33.66	344.02±44.92
p value		NS	NS	<0.01	<0.01
Triglyceride	191.52±25.71	193.77±35.22	197.54±27.33	226.31±38.02	249.21±42.95
P value		NS	NS	<0.01	<0.01
VLDL-C	38.34±5.10	38.75±7.10	39.57±5.43	45.10±7.25	49.84±8.59
p value		NS	NS	<0.01	<0.01
LDL-C	189.33±27.30	189.95±37.72	203.60±25.47	224.58±28.96	255.85±36.90
p value		NS	NS	<0.01	<0.01
HDL-C	35.03±2.36	33.65±3.97	34.86±3.30	31.12±3.38	30.90±2.36
P value		NS	NS	<0.01	<0.01

The increase in the serum cholesterol, triglyceride, VLDL-C and LDL-C levels in Diabetic retinopathy and Diabetic nephropathy was statistically significant ($p<0.01$) as compared to controls. The increased values were not statistically significant in Diabetes mellitus without complications and in Diabetic neuropathy group.

The decrease in the HDL-cholesterol levels in Diabetic retinopathy and Diabetic nephropathy was statistically significant ($p<0.01$) as compared to controls. The decreased values were not statistically significant in Diabetes without complications and in Diabetic neuropathy groups.

Discussion

Diabetes mellitus is a major health problem worldwide. It is a serious debilitating and deadly disease that has now reached epidemic proportions. Higher levels of glycosylated hemoglobin levels and dyslipidemia are major risk factors in development of chronic complications in Diabetes mellitus.

Abnormal glucose homeostasis is the cause of impaired glucose tolerance in Diabetes mellitus. Impaired insulin secretion / resistance, impairs glucose utilization by the insulin sensitive tissues and increases hepatic output of glucose, contributing to hyperglycemia.

There was a statistically significant increase ($p<0.01$) of blood glucose levels in all groups of cases as compared to controls. Our findings are in accordance with the United Kingdom Prospective Diabetic study[1] and also with studies done by Jeevan et al[2] and R.D Ankush et al[3], Ashakiran et al[4], Yiling J. Cheng et al[5].

Estimation of blood glucose is not only of diagnostic importance but also helps in screening of individuals traversing from normal glucose to impaired glucose tolerance to overt Diabetes.

As plasma glucose is consistently elevated, there is an increase in the nonenzymatic glycation of hemoglobin. HbA_{1c} is formed by a nonenzymatic irreversible process of combination of aldehyde group of glucose with the amino terminal valine of the β-chain of hemoglobin. This alteration reflects the glycemic history over the previous 2-3 months. Mean blood glucose levels of past 1 month, 2 months, and 3 months contribute 50%, 40% and 10% respectively to the final HbA_{1c} results. Hence HbA_{1c} can be considered as a best index of metabolic control for Diabetic patients. It has been used as a gold standard for assessing mean glycemia and also a measure of risk for development of Diabetes mellitus related complications.

About 50% individuals with type 2 Diabetes mellitus have one or more Diabetes specific complications at the time of their diagnosis. They are unaware that they have this disorder. HbA1c can help in early initiation of treatment which will help to prevent future metabolic derangements.

Increase in the mean HbA_{1c} level in all groups of cases was statistically significant ($p<0.01$) as compared to controls. Our finding is in accordance with the studies of Jeevan et al [2] and R.D Ankush et al [3], Al-Lawati et al[6] and the UKPDS [1].

Estimation of HbA_{1c} not only helps in the treatment of Diabetes mellitus but also predicts the risk for the development and/or progression of Diabetes associated complications as glycosylated hemoglobin levels reflects average glucose control in the body over the previous 2-3 months.

Type 2 DM is usually associated with dyslipidemia. Elevated levels of serum cholesterol, plasma triglyceride, LDL-C, VLDL-C and decreased levels of HDL cholesterol were seen in all groups of patients as compared to control. The increase in the mean serum cholesterol levels, triglyceride, LDL-C, VLDL-C and decreased levels of HDL cholesterol in Diabetic retinopathy and Diabetic nephropathy was statistically significant ($p<0.01$) as compared to

controls. These findings are in accordance with the studies of Otieno et al[7], Addishu Mengesha[8], NP Suryawanshi[9], and Rajes Qvist et al[10]. The increase was not statistically significant in Diabetic nephropathy and DM without complications group.

In our study the decrease in the mean HDL-cholesterol levels in Diabetic retinopathy and Diabetic nephropathy was statistically significant ($p<0.01$) as compared to controls. The decreased values were not statistically significant in Diabetes mellitus without complications and in Diabetic neuropathy groups. This is in accordance with the study done by Rajes Qvist et al[10], Rema M et al[11] and S Ashok et al[12].

Uncontrolled DM leads to increased levels of FFA, triglycerides and VLDL. Insulin deficiency causes excessive mobilization of free fatty acids (FFA) and underutilization of chylomicrons and VLDL leading to hypertriglyceridemia due to esterification of FFA Impairment of glucose metabolism results in increased flux of free fatty acid from the adipocytes. In the liver, the free fatty acids promote the synthesis of triglycerides and VLDL-Cholesterol. VLDL-cholesterol clearance is also reduced due to decreased activity of insulin sensitive lipoprotein lipase. The increased number of VLDL cholesterol particles and increased plasma triglyceride levels decrease the level of HDL cholesterol and increase the concentration of small dense LDL-cholesterol particles. This explains the occurrence of the characteristic lipid triad of high triglyceride level, high levels of small dense LDL cholesterol and low HDL cholesterol level.

Increased oxidation of free fatty acids leads to increased concentration of acetyl CoA which exceeds the capacity of liver to utilize it in the TCA cycle. Acetyl CoA is further utilized in the synthesis of cholesterol, fatty acids and triglycerides.

Dyslipidemia is associated with both macrovascular and microvascular complications. Decrease in the serum levels of cholesterol, triglyceride, LDL-cholesterol, and increase in the HDL-cholesterol levels may help to delay Diabetes mellitus associated complications.

Laboratory evaluation of lipid profile along with glycosylated hemoglobin in Diabetes mellitus patients aids in early medical intervention, to prevent or delay the microvascular complications of Diabetes mellitus like neuropathy, retinopathy and nephropathy.

Conclusion

Large number of individuals who meet the current criteria for Diabetes mellitus are asymptomatic and unaware that they have one or more diabetic specific complications like retinopathy, neuropathy and nephropathy.

Our study shows that poor glycemic control and dyslipidemia are associated with increased incidence of Diabetic complications like neuropathy, retinopathy and nephropathy.

Estimation of HbA_{1c} and lipid profile in DM patients helps in early detection and timely treatment to prevent DM associated complications. Good glycemic control and maintenance of lipid profile within normal levels by medical intervention should be part of comprehensive diabetes care.

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