



HBA1C AND MICROALBUMIN AS A BIOMARKER FOR EARLY DIAGNOSING TYPE II DIABETES MELLITUS AND ITS ASSOCIATED COMPLICATIONS IN THE RURAL REGION OF VIDARBHA, MAHARASHTRA, INDIA

Sarmistha Sarkar*¹, Ajay Meshram² and Komal Meshram³

^{1,2}Dept. of Biochemistry, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, Maharashtra, 442001, India

³Dept. of Physiology, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, Maharashtra, 442001, India

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a group of metabolic diseases which if not controlled can cause life threatening complications.

Aim: HbA1c and Microalbumin as a Biomarker for early diagnosing Type II Diabetes Mellitus and its associated complications in the rural region of Vidarbha, Maharashtra, India.

Methodology: Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), triglyceride (TG), serum urea, creatinine and microalbuminuria levels were evaluated. Total sample size was 60, which was divided into 30 study group with type II DM who attended the Medicine OPD of AVBRH Hospital and 30 age matched healthy controls included in the study.

Results: Results of serum lipid profile showed higher mean of TC, TG and LDL in patients with diabetes ($p < 0.0001$). Serum urea and creatinine levels were higher in cases as compared to the controls ($p < 0.0001$). Urinary Microalbumin level was 70.71 ± 5.57 which was higher in the cases as compared to controls ($p < 0.0001$). HbA1c has significant negative correlation with HDL and Creatinine ($p < 0.01$).

Conclusion: Early detection of lipid profile and kidney profile abnormalities can minimize the risk for development of cardiovascular and renal complications in the type II diabetic patients.

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both¹. Type II DM is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response and Type II DM, accounts for approximately 90 - 95%. According to the International Diabetic Foundation, currently the disease affects >62 million Indians, which is >7.1% of India's adult population. According to Wild *et al.*² the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030, with maximum increase in India. Due to the alarming increase in the incidence and prevalence of diabetics in India, WHO has declared India as the-Diabetic Capital of the World (Gupta, 2002)³. Chronic hyperglycemia is associated with significant long-term complications like damage to the nerves, heart, blood vessels, eyes and kidneys (Yki-Yarvinen1998)⁴.

Several pathogenetic processes are involved in the development of diabetes. These include processes, which destroy the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin (Report of a WHO Consultation, 1999)⁵.

Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. Often symptoms are not severe, or may be absent.

Diabetes has burdened the health-care system, which is already under strain due to other chronic diseases and the uncontrolled diabetes has lead to an increase in the rate of complications, and thus has increased the cost of treating these patients.

In diabetes, glucose is underutilised and develops clinical hyperglycaemic episodes, such as ketoacidosis or hyperosmolar coma. As the disease progresses, individuals are at risk for the development of specific complications including retinopathy leading to blindness, nephropathy causes renal failure and atherosclerotic heart disease.

*Corresponding author: Sarmistha Sarkar

Dept. of Biochemistry, Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha, Maharashtra, 442001, India

Before people develop Type II diabetes, they almost always have "prediabetes" –bloodglucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes. Recent research has shown that some long-term damage to the body, especially the heart and circulatory system, may already be occurring during prediabetes (DePaula, 2008)⁶.

Diabetes is associated with adverse health outcomes like dementia, falls, fall-related fractures, cardiovascular events, poor quality of life, and increased mortality. Diabetes mellitus increases the risk of dyslipidemia, there is an elevated triglyceride level and a decreased HDL cholesterol level is seen commonly⁷. Diabetes is associated with a greater risk of morbidity and mortality from cardiovascular disease (CVD). An early intervention to normalize circulating lipid levels has been shown to reduce cardiovascular complications and mortality (Windler, 2005)⁸. Serum lipids are frequently abnormal and are likely to contribute to the risk of coronary artery disease⁹. Atherosclerosis is characterised by the deposition of cholesterol into the artery wall. Atherosclerosis accounts for around 80% of all deaths among diabetic patients. Prolonged exposure to hyperglycaemia is now recognized a major risk factor in the pathogenesis of atherosclerosis in diabetes. Hyperglycaemia induces a large number of alterations at the cellular level of vascular tissue that potentially accelerate the atherosclerotic process. There are three major mechanisms that encompass most of the pathological alterations observed in the diabetic vasculature- 1) Nonenzymatic glycosylation of proteins and lipids, which can interfere with their normal function by disrupting molecular conformation, alter enzymatic activity, reduce degradative capacity and interfere with receptor recognition; 2) Oxidative stress; and 3) Protein Kinase C (PKC) activation with subsequent alteration in growth factor expression. Worsening of glycemic control deteriorates lipid abnormalities in diabetes mellitus¹⁰. According to the American Diabetes Association (ADA) HbA1c level of <7% is the goal of optimal blood glucose control¹¹ and the American Association of Clinical Endocrinologist has further recommended HbA1c level of <6.5% is the target goal¹². Criteria for abnormal lipid profiles were based on the ADA criteria, Hypercholesterolemia refers to a total cholesterol level ≥ 200 mg/dl, Hypertriglyceridemia refers to a level is ≥ 150 mg/dl, HDL was considered low when the level is < 40 mg/dl in males and < 50 mg/dl in females, LDL was considered high when the level is ≥ 100 mg/dl. The glycated hemoglobin (HbA1c) provides an index of average blood glucose level during the past 2–3 months and considered to be the most reliable measure of long-term metabolic control of blood glucose level in type II diabetes mellitus (Nathan 1984)¹³. HbA1c is formed by the condensation of glucose with the N-terminal Valine residue of each β -chain of HbA to form an unstable Schiff-base, which is the most widely used as the long-term glycemic control, as well as an independent risk factor for cardiovascular diseases (stroke)¹⁴. American Diabetes Association (ADA) proposed the use of HbA1c in the definition of diabetes and the category of increased diabetes risk (which also includes impaired fasting glucose and impaired glucose tolerance) in 2010 (American Diabetes Association Diabetes Care 2010)¹⁵. Estimated risk of CVD has shown to be increased by 18% for each 1% increase in absolute HbA1c value in diabetic population (Selvin, 2004)¹⁶. Lower HbA1c values, has been shown to delay the onset and

slow the progression of diabetic retinopathy, nephropathy, and neuropathy in Diabetes¹⁷. People with type II diabetes develop severe renal and cardiovascular complications early, especially those with high urinary albumin excretion¹⁸. Nelson *et al*¹⁹ identified multiple factors contributing to the initiation and progression of diabetic nephropathy including proteinuria, hyperglycemia, hypertension, genetic susceptibility, ethnicity, high protein intake and familial predisposition to renal disease. Longer the duration of diabetes, higher the frequency of diabetic nephropathy.

Even though Diabetes is prevalent in India, studies are lacking to find out the risk of developing diabetic complications like cardiomyopathy and nephropathy in type II Diabetics. Our study is a rural hospital based study and it will provide the necessary insight into the situation. We aimed HbA1c and Microalbumin as a Biomarker for early diagnosing Type II Diabetes Mellitus and its associated complications in the rural region of Vidarbha, Maharashtra, India. The study was carried out in the Department of Biochemistry in association with Department of Medicine, Jawaharlal Nehru Medical College and Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha, Maharashtra, India.

MATERIALS AND METHODS

A comparative and cross-sectional study was conducted. Institutional Ethical Committee approved the study. The study was done from June 2017 to November 2017, total sample size 60 including males and females and divided into two groups. Informed written consent was taken for the study purpose. 30 study group with type II DM who attended the outpatient clinic of the Medicine Department of AVBRH Hospital, Sawangi (Meghe), Wardha, India and 30 age and sex matched healthy controls. All patients with known history of type II DM within the age group of 35-70 years included in the study. Information about subject's age, sex, lifestyle, family history of diabetes and other chronic diseases/disorders were written in pre-design format. HbA1c assay was done by immunoassay method, fasting blood glucose by GOD/POD method²⁰, total cholesterol by enzymatic endpoint method²¹, triglycerides liquid stable GPO-POD method²², HDL direct enzyme method, LDL using Friedewald formula, VLDL by appropriate formula, Urea by kinetic method, Creatinine by JAFFE (Enzymatic) method and Microalbumin by Immunoturbidimetric method - all measured by Randox auto-analyzer on the same day of collection.

Sample Collection

3ml blood sample was collected from each subject. Fasting blood sample in sterile fluoride bulb for FBS, plain bulb for lipid profile, urea, creatinine, and in EDTA bulb for HbA1c under all the aseptic conditions with consent of the patient. Spot morning urine sample – collected for urinary micro albuminuria. Blood Sample was allowed to stand for clotting for 25 to 30 minutes. Serum was separated by centrifuging blood at 3000rpm for 10 mins.

Inclusion Criteria

All patient with known history of type II DM, age group between 35-70 years and diabetic patients, those who gave the consent for the study were included in the study.

Exclusion Criteria

Patient with major illness like liver disease, renal failure, cardiovascular disease, which can directly or indirectly affect the result, previous or current treatment with drugs known to interfere with glucose and lipid metabolism were excluded from the study. Chronic alcoholics and chronic smokers are also excluded from the study.

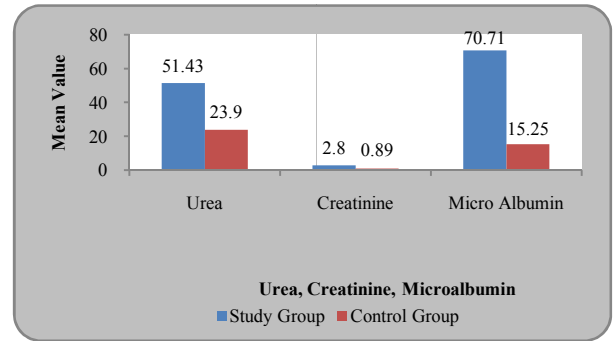
Statistical Analysis

Statistical analysis was done by using descriptive and inferential statistics using Student’s unpaired t test and Pearson’s Correlation Coefficient and software used in the analysis were SPSS 17.0 version and EPI-INFO 6.0 version and $p < 0.05$ is considered as level of significance.

RESULTS

Table 1 shows results of serum lipid profile showed that the mean values for TC, TG, HDL, LDL and VLDL in study group were 228.50 ± 30.75 , 152.10 ± 40.98 , 40.73 ± 6.58 , 153.13 ± 27.74 and 33.33 ± 9.93 mg/dL, respectively. TC, TG and LDL level were significantly higher in the cases as compared to controls ($p < 0.0001$).

the cases as compared to the controls ($p < 0.0001$). Mean value for urea, creatinine and Microalbumin levels in the study group were 51.43 ± 5.31 , 2.80 ± 0.48 , 70.71 ± 5.57 respectively, which were significantly higher in the cases as compared to the controls ($p < 0.0001$). Table 2 shows HbA1c has significant negative correlation with HDL and Creatinine ($p < 0.01$).

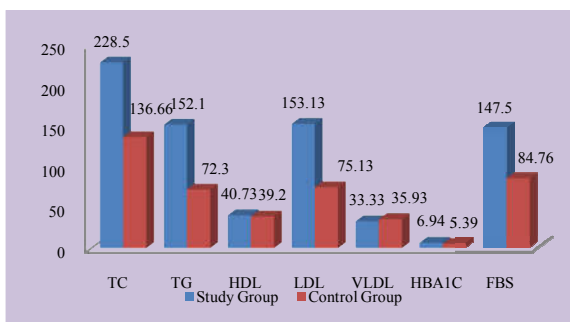


Graph 2 Comparison of Urea, Creatinine and Microalbumin levels in two groups

Table 1 Comparison of biochemical parameters in two groups

	Group	N	Mean	Std. Deviation	Std. Error Mean	t-value	p-value
TC	Study	30	228.50	30.75	5.61	16.05	0.0001,S
	Control	30	136.66	5.964	1.08		
TG	Study	30	152.10	40.98	7.48	10.62	0.0001,S
	Control	30	72.30	3.56	0.65		
HDL	Study	30	40.73	6.58	1.20	1.06	0.29,NS
	Control	30	39.20	4.37	0.79		
LDL	Study	30	153.13	27.74	5.06	15.11	0.0001,S
	Control	30	75.13	5.36	0.97		
VLDL	Study	30	33.33	9.93	1.81	1.14	0.25,NS
	Control	30	35.93	7.57	1.38		
HbA1c	Study	30	6.94	0.47	0.08	16.26	0.0001,S
	Control	30	5.39	0.23	0.04		
FBS	Study	30	147.50	31.23	0.52	29.43	0.0001,S
	Control	30	84.76	36.27	0.59		
Urea	Study	30	51.43	5.31	0.97	21.58	0.0001,S
	Control	30	23.90	4.53	0.82		
Creatinine	Study	30	2.80	0.48	0.08	19.73	0.0001,S
	Control	30	0.89	0.20	0.03		
Microalbumin	Study	30	70.71	5.57	1.01	48.34	0.0001,S
	Control	30	15.25	2.89	0.52		

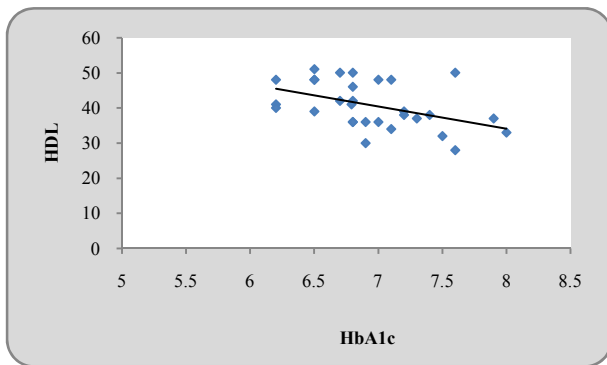
Mean value for HbA1c in the study group was 6.94 ± 0.47 , which was significantly higher in the cases as compared to the controls ($p < 0.0001$) and the mean value for FBS in the study group was 147.50 ± 31.23 , which was significantly higher in



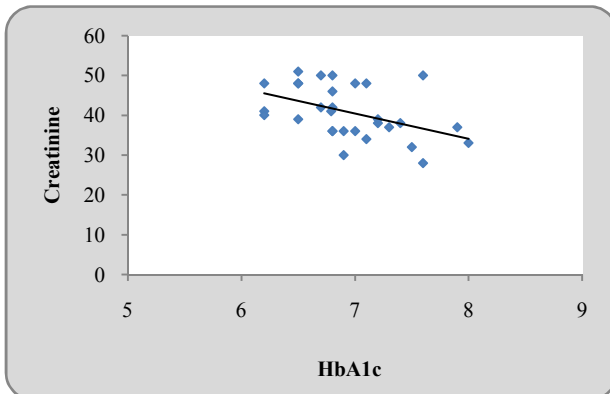
Graph 1 Comparison of Lipid Profile, HbA1c and FBS in two groups

Table 2 Correlation of HbA1c with other parameters in study group

	Mean	Std. Deviation	N	Correlation 'r'	p-value
HbA1c	6.94	0.47	30	-	-
TC	228.50	30.75	30	0.08	0.65,NS
TG	152.10	40.98	30	0.16	0.39,NS
HDL	40.73	6.58	30	-0.45	0.01,S
LDL	153.13	27.74	30	0.14	0.44,NS
VLDL	33.33	9.93	30	0.10	0.59,NS
FBS	147.50	31.23	30	0.08	0.65,NS
Urea	51.43	5.31	30	0.16	0.39,NS
Creatinine	2.80	0.48	30	-0.45	0.012,S
Micro Albumin	70.71	5.57	30	0.12	0.51,NS



Graph 3 Correlation of HbA1c with HDL in study group



Graph 4 Correlation of HbA1c with Creatinine in study group

DISCUSSION

The present study was carried out at AVBRH and JNMC, Sawangi (Meghe), Wardha, India. The findings are as follows- HbA1c, TC, TG, HDL and LDL levels were found higher in the cases as compared to controls, which is in accordance with the study of Wexler *et al*²³.

In our study, positive correlations were observed between serum levels of TC, TG, LDL, VLDL with HbA1c, which is in accordance with the study of Erciyas *et al*, (2004).²⁴ HbA1c shows significant negative correlation with HDL and creatinine ($p < 0.01$).

Diabetic patients with elevated HbA1c and altered lipid profile considered as a very high risk group for severe complications. Improving glycaemic control can reduce the risk of various complications in diabetic subjects.²⁵ According to the Diabetes Complications and Control Trial (DCCT) HbA1c is the gold standard of glycaemic control and the level of HbA1c value $\leq 7.0\%$ was said to be appropriate for reducing the risk of cardiovascular complications.²⁶

It has also been showed in previous study conducted by Khaw *et al* that by reducing the level of glycated hemoglobin (HbA1c) by 0.2% could lower the mortality rate by 10%.²⁷ Goldberg in their study showed that the cause of altered lipid profile in type II diabetes maybe due to the insulin is not working properly or secreted in a proper manner, which can affect the production of liver apolipoprotein.²⁸

HbA1c reflects average blood glucose concentration over the course of the RBC lifespan in normal individuals. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial indicated an increased hypoglycemia risk in type II diabetic participants with poorer glycaemic control compared with

subjects with desirable HbA1c levels²⁹. HbA1c is the most widely used biomarker for long-term glycemic status, as well as an independent risk factor for coronary heart disease (CHD) and stroke³⁰.

Defective insulin secretion leads to various metabolic diseases in Type II diabetes, spanning from hyperglycemia due to defective insulin-stimulated glucose uptake and up regulated hepatic glucose production, along with dyslipidemia, which includes impaired homeostasis of fatty acids, triglycerides, and lipoproteins³¹.

Rudberg *et al*³², in a study of adolescents with a mean duration of disease of 10.9 years, found that the duration of disease was an important factor in the overall severity of glomerulopathy. Diabetic nephropathy is a clinical hall mark of microangiopathy and is the most important single disorder leading to renal failure in adults³³. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels of albumin in the urine. In addition to its being the earliest manifestation of nephropathy, microalbuminuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with type II diabetes. Thus, the finding of microalbuminuria is an indication for screening for possible vascular disease and aggressive intervention to reduce all renal and cardiovascular risk factors.

In our study serum Urea and Creatinine concentration was found significantly higher in the cases as compared to the controls ($p < 0.0001$). A research conducted by Anjaneyulu *et al* 2004 had found that increase urea & serum creatinine in diabetic rats indicate progressive renal damage³⁴. Serum Urea and Creatinine are the established marker of Glomerular Filtration Rate (GFR). Serum Creatinine is although a more sensitive index of kidney function compared to the Urea. It is because it fulfills the requirements of a perfect filtration marker according to Perrone *et al*.³⁵

In our study there is significant increase in urinary Microalbumin levels in the cases as compared to the controls ($p < 0.0001$). The causal risk factors for microalbuminuria are raised blood pressure and poor glycaemic control. Some studies have revealed duration of diabetes, male sex, and pre-existing retinopathy as major risk factors for microalbuminuria.³⁶ In our study, multiple logistic regression analysis revealed age, duration of diabetes, HbA1c, and fasting plasma glucose as the risk factors for microalbuminuria. Gupta *et al* reported HbA1c to be associated with microalbuminuria.³⁷ The association of glycaemic control with microalbuminuria has been well established by various studies.^{36,38}

CONCLUSION

The prevalence of Type II diabetes mellitus is increasing day by day and is associated with a very high morbidity and mortality rate, reduced quality of life and high costs of treatment, despite intensive insulin treatment. HbA1c can be use as a predictor of dyslipidemia and early detector of diabetic complications in addition to glycaemic control. Lipid profile, Kidney profile estimation and screening for microalbuminuria will allow the identification of patients with nephropathy and cardiovascular complications at very early course of the disease. So HbA1c and microalbumin are the important biomarkers to diagnose the risk of diabetic

complications- like cardiomyopathy and nephropathy in the type II diabetic subjects.

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