

Association between Serum Lipid Profile and Glycated Hemoglobin in Middle Aged Pre-Diabetic Individuals: The Bangladesh Study

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Abstract

Diabetes Mellitus is one of the leading non-communicable diseases all over the world including Bangladesh. Diabetes is often preceded by a prodromal condition termed pre-diabetes. Pre-diabetes is a condition in which the blood glucose level is above normal but below the diagnostic threshold for diabetes mellitus. Impaired lipid profile is commonly present in type 2 diabetes and can also occur in pre-diabetes. The present study was undertaken to evaluate the association between serum lipid profile and glycated hemoglobin in pre-diabetic individuals in middle-aged Bangladeshi subjects. This observational cross sectional study was carried out in the department of Biochemistry, Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) hospital, from July 2013 - June 2014. A total 131 subjects of age within the range of 30-45 years were selected for the purpose and classified into apparently healthy control (n=62), pre-diabetes (n= 69) groups based on the values of OGTT. Blood glucose – both fasting and 2hr after glucose, HbA1C, total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol level were measured in all study subjects. Among the middle aged Bangladeshi subjects attending BIRDEM hospital, mean±SD of HbA1c values were 5.3±1.1% in control group and 5.9±1.2% in pre-diabetes. There was no significant difference in total cholesterol, triglyceride, HDL-c and LDL-c in patients with normal and Pre-diabetic individuals. According to this study, HbA1c value does not correlate well with total cholesterol, triglyceride and LDL-c (p=0.47, 0.93, 0.49) in patients with pre-diabetic individuals. Studies on larger population are required to determine the prognostic implication of routine lipid profile.

Keywords: Pre-diabetes, HbA1C, Total cholesterol (TC), Triglyceride (TG), High density lipoprotein (HDL-C) cholesterol, Low density lipoprotein (LDL-C) cholesterol.

Introduction

Diabetes mellitus has become a global pandemic, generating overwhelming costs and burdens upon patients as well as health care providers. In Bangladeshi population, 8.4 million people have diabetes with a prevalence rate of 9.6%, which is expected to reach 11 million by 2030 (International Diabetes Federation). The pathological complications of this disease are associated with increased mortality and morbidity [1-4]. Pre-diabetes is a condition in which the blood glucose level is above normal but below the diagnostic threshold for diabetes mellitus [5]. According to National diabetes fact sheet 2011, in United States 79 million people were in pre-diabetic phase. The American Diabetes Association reports that approximately 11% of people with pre-diabetes who receive no treatment or intervention will develop type 2 diabetes every year [6].

Impaired glucose metabolism includes two conditions: Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT). IFG is a condition when fasting blood glucose levels are higher than normal but below the cut off used for diagnosing diabetes mellitus i.e. 110-125 mg/dl (6.1-6.9 mmol/l) while IGT, a condition when 2 hr postprandial blood sugar level are higher but still below the cut off used for diagnosing diabetes between i.e. 140-199 mg/dl (7.8-11.0 mmol/l). Pre-diabetes are characterized by either impaired fasting glucose and impaired glucose tolerance or glycated hemoglobin (HbA1c) level between 5.7%-6.4% or both [7].

Pre-diabetes is multi factorial and common risk factors includes being overweight especially those who have excess weight around the waistline, physical inactivity, dyslipidemia (high triglycerides and low high density lipoprotein cholesterol and/ or high total cholesterol), high blood pressure, polycystic ovarian syndrome, gestational diabetes, family history of type 2 diabetes and/or heart disease. Pre-diabetes occurs 73.4% more frequently in people with family history of diabetes as compared to those without family history [8].

Pre-diabetics are considered to be at higher risk of having low level of high density lipoprotein cholesterol (HDL-c), increased level of low density lipoprotein cholesterol (LDL-c), high triglyceride (TG), and hence are at higher risk of cardio vascular disease (CVD). Impaired lipid profile i.e. dyslipidemia is commonly associated with CVD in type2 diabetes and can also occur in pre-diabetics. According to Saudek CD et al, (2008) macro vascular and micro vascular complications can start in pre-diabetic individuals with IFG or IGT [9]. Early detection of impaired lipid profile in pre-diabetic phase will reduce the risk of CVD and its complications.

Commonly used tests for the diagnosis of diabetes include measurements of fasting plasma glucose levels and the oral glucose tolerance test (OGTT). Recently, hemoglobin A1C (A1C) level of $\geq 6.5\%$ has been included as a criterion for diabetes diagnosis by the American Diabetes Association [10]. Precise estimates of progression rates from 'pre-diabetes' to type 2 diabetes are needed to optimize prevention strategies for high-risk individuals. In the case of diabetes, the major outcome of interest is the long term micro vascular complication, leading to the endorsement of HbA1C for diagnosis in many countries worldwide, with some variations in cut-offs and test strategies [11]. IGT and IFG are associated with a substantially increased risk of developing diabetes with the highest risk in people with combined IFG and IGT. Considered IGT is more common than IFG in most population and it is more sensitive for identifying people who will develop diabetes [12]. The laboratory based HbA1C test can be used to be diagnosing both conditions providing the physician with another way to identify undiagnosed diabetes and thus treat patients before problems develop or worsen [13].

The 2010 American Diabetes Association (ADA) standards of care for diabetes, based largely on the opinion of an international expert committee, added hemoglobinA1C (HbA1C) as diagnostic criteria for diabetes ($\geq 6.5\%$) and pre-diabetes (5.7–6.4%) [14,15]. The inclusion of HbA1C as a diagnostic tool will increase the feasibility and dissemination of diabetes screening because it eliminates the need for fasting blood glucose.

Compared with glucose measurements, the use of HbA1C as a diagnostic test has certain advantages, including convenience, less day-to-day variability, greater pre-analytical stability, and international standardization [14,15]. For more than a decade, it has been recognized that there may be discordance between HbA1C and other measures of glycaemia. The use of HbA1C for diabetes diagnosis is based on the hypothesis that HbA1C is a true and consistent measure of mean blood glucose [16]. HbA1C estimation is better than fasting blood glucose estimation for determining risks of cardiovascular disease and death from any cause [17].

In this study we have taken WHO criteria to diagnose diabetes and pre-diabetes and estimated the fasting lipid profile in same patients. Very few literatures are available about the association between serum lipid profile and glycated hemoglobin in pre-diabetic individuals. To our knowledge no such study is available in Bangladesh where diabetes is now declared as an epidemic and prevalence of pre-diabetes is also high especially in urban population. The aim of this study was to compare total cholesterol, triglyceride, HDL-c, and LDL cholesterol levels in pre-diabetic subjects with HbA1C.

Materials and methods

This observational cross sectional study was carried out in the department of Biochemistry, BIRDEM from July 2013 - June 2014. A total of 131 subjects aged 30-45 years were selected purposively from the outpatient department of BIRDEM. Among them 62 participants had normal fasting and postprandial blood glucose (control), while 69 participants had pre-diabetes (IFG/IGT) based on OGTT. Patients suffering from hemoglobinopathies, iron deficiency anemia, hemolytic anemia and pregnancy were excluded from the study. Ethical approval of the study was from the Ethical Review Committee of the Bangladesh Diabetic Somiti (BADAS). Informed written consent was obtained from each of the participants after explaining the objective of the study. Data were collected including demographic characteristics and clinical history by utilizing a pre-designed questionnaire and were collected by direct interview from participants. Relevant physical examinations were performed on all participants. With all aseptic precaution about 5 ml blood was collected from all of the subjects. Serum was separated after centrifuging at 3000 rpm for 10 minutes. Blood glucose – both fasting and 2hr after glucose, HbA1C, Total cholesterol, Triglyceride, High density lipoprotein (HDL) cholesterol, Low density lipoprotein (LDL) cholesterol level were measured in all participants. HbA1C was analyzed by high pressure liquid chromatography (Biorad D10). All the biochemical tests were done in the Department of Molecular and Cell Biology, BIRDEM following standard methods and procedures.

Data were expressed mean (\pm SD) and number (percent) as appropriate. Statistical tools, chi-square, unpaired Student's t-test were performed to establish statistical difference between groups as applicable. Statistical calculations were performed using Statistical Package for Social Sciences (SPSS) - version 11.5. P value ≤ 0.05 was taken as level of significance.

Results

A total number of 131 subjects were recruited in the study. Among them 62 were healthy controls, and 69 had pre-diabetes. Sex distribution of the study subjects is presented in Table-I. In the control group, 38 were males and 24 were females with an age range of 30-45 years. Pre-diabetes groups included 44 males and 25 females of the same age range.

Table I: Distribution of the study subjects on the basis of gender.

Gender	Control	Pre diabetes
	n (%)	n (%)
Male	38(61.3)	44(63.8)
Female	24(38.7)	25(36.2)
Total	62(100)	69(100)

Data were expressed as number (percent).

Table II presents clinical variables of the subjects. Clinical variables including age, body mass index (BMI), waist hip ratio (WHR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) was observed in the study subjects. No significant difference was observed in control versus Pre-diabetes group except for DBP. Table III shows biochemical variables. Significant differences were only observed in fasting (mmol/L), 2hr after glucose (mmol/L) and

HbA1C (%) in two groups. However, no significant differences were observed in TG (mg /dl), TC (mg /dl), HDL-c (mg /dl) and LDL-c (mg /dl).

Table II: Clinical variables of the study subjects.

Clinical variable	Control (n=62)	Pre-diabetes (n=69)	p-value
Age (yr)	40.9 ±2.9	41.9 ±2.7	0.4
BMI (kg/m ²)	22.0±3.3	22.5±3.9	0.43
WHR	1.11±0.2	1.0±0.1	0.17
SBP(mmHg)	137±32	151±28	0.05
DBP(mmHg)	82±14	89±19	0.01

Results expressed as mean±SD; SD, Standard deviation; n, number of subjects; WHR, waist hip ratio; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; BMI, Body mass index; t-value/p-value, t-test/p-value. Unpaired Student's t-test was performed to calculate statistical difference between groups. P value <0.05 was taken as level of significance.

Table III: Biochemical variables of the study subjects.

Variable	Control (n=62)	Pre-diabetes (n=69)	p-value
	mean±SD	mean±SD	
FBG (mmol/L)	4.8±0.62	5.7±0.61	0.0001
2hABG(mmol/L)	5.1±0.9	8.72 ± 2.6	0.0001
HbA1C (%)	5.3±1.1	5.9 ± 1.2	0.004
TG (mg /dl)	162±84	155±84	0.72
TC (mg/dl)	202.7±41.2	198.6±34.9	0.53
HDL-c (mg /dl)	39.3±9.3	40.9±9.1	0.32
LDL-c (mg/dl)	136.5±39.7	139.9±35.4	0.60

Results expressed as mean±SD; SD, Standard deviation; n, Number of subjects; %, Percentage; FBG, Fasting blood glucose; 2hABG, 2 hours after blood glucose; TG, Triacylglycerol; TC, Total cholesterol; HDL-c, High density lipoprotein cholesterol; LDL-c, Low density lipoprotein cholesterol. ;t-value/p-value, t-test/p-value. Unpaired Student's t-test was performed to calculate statistical difference between groups. P value <0.05 was taken as level of significance

Table IV presents correlation of HbA1c with lipid profile in pre-diabetic subjects. There is no significant correlation of HbA1c value with total cholesterol, triglyceride and LDL-c (p=0.47,0.93,0.49) in patients with pre-diabetic individuals.

Table IV: Correlation of HbA1c with lipid profile in pre-diabetic subjects.

		HbA1c	T_Chol	HDL	LDL	TG
HbA1c	r	1	-0.88	0.266*	-0.83	0.009
	p		0.470	0.027	0.497	0.939
T_Chol	r		1	-0.066	0.478**	.072
	p			0.591	0.000	0.558

HDL	r			1	-.231	0.097
	p				0.056	0.427
LDL	r				1	0.008
	p					0.947
TG	r					1
	p					

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Discussion

Diabetes has become a major health problem in the world. The prevalence of diabetes and its adverse health effects is increasing more rapidly in South Asia than in any other large region of the world. No significant difference was seen in BMI, WHR in both the groups (p=0.43, 0.17). There was no significant difference in mean levels of triglyceride, total cholesterol, HDL-c, and LDL cholesterol levels (p=0.72, 0.53, 0.32, 0.60) between control and pre-diabetic patients. There was no significant correlation of HbA1c value with total cholesterol, triglyceride and LDL-c (p=0.47, 0.93, 0.49) in patients with pre-diabetic individuals.

Conventionally oral glucose tolerance test is performed in diagnosis of blood glucose abnormality. However, random blood glucose is performed to evaluate individual blood glucose control and its state in undiagnosed person. These two procedures found to have its limitations. OGTT is often inconvenient for individuals since it requires couple of hours to complete the procedure and the random blood glucose estimation often mislead the clinician and health workers owing to the poorly interpretable results. An easily performed and sensitive test is at utmost important to diagnose diabetes/ blood glucose abnormality.

The hemoglobin A1C test - also called HbA1C, glycated hemoglobin test, or glycohemoglobin - is an important test used to evaluate glycemic control over a period of 3-4 months. Blood sample may be drawn at any time of the day. The test procedure does not take long time, sampling is easier and samples are more stable. Considering the limitations of OGTT different bodies, working for diabetes, were looking for single and sensitive test to diagnose hyperglycemia. In June 2009, the International Expert Committee, which represents several major diabetes groups, recommended using HbA1C to diagnose diabetes [18].

Genetic variants (e.g. Hbs trait, Hbc trait), elevated fetal hemoglobin and less common Hb variants like HbE and derivatives can affect the accuracy of HbA1C measurements [19]. Hemoglobin E (HbE) is found in the eastern half of Indian subcontinent and throughout South East Asia, where in some areas, carrier rates are as high as 60% of the population [20]. It is the second most prevalent hemoglobin variant worldwide, mostly found in the Far East and Southeast Asia [21]. More than 1000 hemoglobin variants have been identified with many of them being clinically silent [22]. Therefore, a falsely high or low HbA1C value caused by the presence of a clinically silent hemoglobin variant may lead to over or under treatment of diabetic patients. So we exclude this type of patients from our study.

In this study no significant difference in lipid profile variable was observed in pre-diabetic patients with normal subjects. Our findings are contrary to the findings of Anjaneya PV et al, but in

their study cut off used for fasting blood glucose was > 100 mg/dl for pre-diabetics [23]. We observed no significant difference in HDL-c while Botnia-study showed low HDL-c in pre-diabetics with IFG [24]. A possibility for the difference in our findings could be geographical and ethnic factors leading to a necessity for a different cut off value for pre-diabetes in Bangladeshi population, as compared to Western or Caucasian population. We recommend a study to evaluate whether the cut off provided by American Diabetes Association should be modified for Bangladeshi population as such a parameter may be affected by race/ethnicity. On long term follow up approximately one-third pre-diabetics convert to type 2 diabetes, one-third remain in pre-diabetic phase while one-third convert back to normoglycemia. We would like to recommend long term study to look for any correlation between dyslipidemia and progression to full blown diabetes among pre-diabetic patients. Further studies are also required to find out the association between dyslipidemia and IFG and a normal fasting blood glucose level.

Conclusion

The present data concluded that HbA1c value does not correlate well with lipid profile in patients with pre-diabetic individuals. Studies on large population are required to find out whether estimation of lipid profile in pre-diabetic should be used routinely or not in pre-diabetic patients.

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