Original Article

Relationship of HbA1c and Blood Lipids in Subjects with Type 2 Diabetes Mellitus

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Abstract

Background*: Diabetes mellitus is a global problem. In diabetic subjects, blood glucose levels are elevated and HbA1c formation is increased. Estimation of HbA1c every two to three months is a measure of glycemic control. Blood lipid levels also undergo derangements in diabetic patients.* ***Objective****: We designed this cross-sectional study to explore any relationship of HbA1c with different blood lipids.* ***Materials and Methods****: This cross-sectional study was done in Bangladesh Institute of Health Sciences General Hospital during the period of January to December 2013. In this study 1253 type 2 diabetic subjects, both male and female, were included. Both male and female subjects were divided into three groups based on HbA1c levels. Total cholesterol, triglycerides and HDL-cholesterol levels of all subjects were measured by standard methods. LDL-cholesterol levels were calculated. All these parameters were compared among groups and their correlation with HbA1c was found.* ***Results****: Total cholesterol, triglycerides and LDL-cholesterol increased with increase in HbA1c% in both males and females; HDL-cholesterol showed no change in females, but in males it decreased with increase in HbA1c%.* ***Conclusion****: The findings of this study suggest that HbA1c% can be used as a biomarker of relative increase of total cholesterol, triglycerides and LDL-cholesterol in diabetic subjects.*

Key words*: HbA1c; Total cholesterol; Triglycerides; HDL-cholesterol; LDL-cholesterol*

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Introduction

Diabetes mellitus is now a global problem. It is a syndrome of impaired carbohydrate, fat and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of tissues to insulin.[1]

Therapy for diabetes requires the long-term maintenance of blood glucose level as close as normal level to minimize the risk of long-term vascular consequences.[2,3] A single blood glucose measurement is an indication of the patient's immediate past condition in hours, but may not represent the true status of blood glucose regulation.[4,5] So, the estimation of hemoglobin A1c (HbA1c) every two to three months has been accepted as a measure of glycemic control of the diabetic patients.

HbA1c is a glycated protein formed by nonenzymic attachment of sugars to Hb.[6] When blood glucose

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enters the erythrocytes, it is attached to ε-amino group of lysine and the amino terminals of hemoglobin. Normally 5% of Hb is glycated and this glycation is proportional to blood glucose concentration. In patients with diabetes mellitus whose blood sugar levels are elevated, formation of HbA1c is increased. Since the half-life of red blood cells is around 60 days, the HbA1c level reflects the mean blood glucose concentration of the period preceding 6−8 weeks.[6,7] Therefore measurement of HbA1c provides valuable information for management of diabetes mellitus.

When glucose attaches to a protein, intermediate products formed include Schiff bases. These can further rearrange by the Amadori rearrangement to ketoamines. The end-products of glycation reactions are termed advanced glycation end-products (AGEs).[6] AGEs cause tissue damage in diabetes mellitus, in which consistent elevation of blood glucose promotes increased glycation.[6] Glycation of collagen and other proteins in the extracellular matrix (ECM) alters their properties (eg, increasing the cross-linking of collagen). Cross-linking can lead to accumulation of various plasma proteins in the walls of blood vessels; in particular, accumulation of low-density lipoprotein (LDL) particles can contribute to atherogenesis. AGEs also appear to be involved in both microvascular and macrovascular damage in diabetes mellitus and are also involved in other processes, such as aging.[6]

The endothelial cells of blood vessels and macrophages have AGE receptors on their surfaces.[6] Uptake of glycated proteins by these receptors can activate the transcription factor NF-kB, generating a variety of cytokines and pro-inflammatory molecules.[8] It is thus believed that AGEs are significant contributors to some of the pathologic findings found in diabetes mellitus.

In diabetic patients, there is also derangement of blood lipids. “Blood lipids” is the term used for all the fatty substances found in the blood, including cholesterol and triglycerides. Cholesterol is a fatty substance which is produced when the liver breaks down saturated fats in food. This cholesterol then passes into the blood in two forms: ‘low density lipoproteins’ (LDLs) which is often called ‘bad cholesterol’ as it helps to deliver cholesterol to the body through the bloodstream and another is ‘high density lipoproteins’ (HDLs) which is known as ‘good cholesterol’ as it helps to take bad cholesterol out of the bloodstream.[9] Triglycerides are another type of fat found in the blood which mainly comes from food. The liver can also convert excess calories into triglycerides. These triglycerides are released into blood and are then transported through body and used as energy or stored as fat.

Having high levels of fat in blood can lead to fatty deposits in the blood vessels in the body, including the coronary arteries. This leads to the narrowing or hardening of the coronary arteries.

Dyslipidemia is common in DM, as both insulin deficiency and resistance affect enzymes and pathways of lipid metabolism.[10] Characteristic abnormalities in lipids in DM include elevated triglyceride (TG) levels, decreased atheroprotective high density lipoprotein-cholesterol (HDL-C) levels, and increased levels of small dense low density lipoprotein-cholesterol (sdLDL-C).[11] Lipoprotein abnormalities contribute substantially to the increased risk of macrovascular disease. Hyperglycemia impairs removal of triglyceride-rich lipoproteins, the accumulation of which aggravates hypertriglyceridemia.[12]

Dyslipidemia can increase the risks of coronary artery disease (CAD) significantly by aggravating the process of atherosclerosis. A direct correlation between HbA1c and the severity of CAD in diabetic patients has been observed.[13] Thus elevated HbA1c has been proposed as an independent risk factor for both diabetics and CAD patients.[14] The American Diabetes Association (ADA) estimated that the risk of diabetes-related mortality increased 25% for each 1% increase in HbA1c.[15] Stabilization of blood glucose levels along with reduction in TG and LDL and increase in HDL would significantly reduce cardiovascular events and mortality in diabetic patients.[16]

As there are very few studies on relationship of HbA1c and blood lipids and these studies are not consistent, we designed this study to find out any relationship between HbA1c% and blood lipids and also to observe correlation of TC, TG, HDL-chol and LDL-chol with HbA1c%.

Materials and Methods

This cross-sectional study was conducted in the department of Clinical Biochemistry, Bangladesh Institute Health Sciences (BIHS) General Hospital, Dhaka during the period January to December 2013. One thousand two hundred fifty three study subjects, both male and female, with type 2 diabetes mellitus were randomly selected from patients attending the outpatient department of BIHS General Hospital, Dhaka advised for biochemical investigations. Specimens were collected after overnight fasting for 10−12 hours. Type 2 diabetes was diagnosed according to WHO criteria[17]. Fasting plasma glucose levels and postprandial venous plasma glucose levels 2-hours after 75 gm oral glucose load were considered. Diabetes was defined if fasting plasma glucose level was equal or above 7.0 mmol/L or 2-hour postprandial plasma glucose ≥11.1 mmol/L. HbA1c levels were determined by modified high performance liquid chromatography (HPLC) method by using D-10 HbA1c analyzer of BIO-RAD, USA. Serum total cholesterol, triglycerides were measured spectophotometrically using Dimension RxL Max (Siemens Healthcare Diagnostic Inc., USA) and HDL-cholesterol was measured by a direct homogenous assay using RxL Max (Siemens Healthcare Diagnostic Inc., USA). All these were measured with proper quality control. LDL-cholesterol was calculated by Friedewald's formula.[18]

Out of the total subjects 610 were males and 643 were females. Age of the subjects was 51 ± 12 and 50 ± 12 years for males and females. Both males and females were divided into 3 (three) groups based on their HbA1c levels. Subjects with HbA1c <7% were in Group A, with HbA1c 7−10% were in Group B and subjects with HbA1c >10% were in Group C. Blood lipids among the groups were compared by one way ANOVA test. Correlation of lipid parameters with percentage of HbA1c was found by Pearson's correlation coefficient test. GraphPad Prisom 6.01 version was used for statistical analyses.

Results

Table I shows the mean age, sex distribution, mean HbA1c and mean concentrations of different circulating blood lipids. Figures 1, 2, 3 and 4 show correlation of TC, TG, HDL-chol and LDL-chol with HbA1c% in male and female subjects. There was significant relationship of these lipid parameters with HbA1c in males ($r=0.201$, $p<0.001$ for TC; $r=0.106$, $p<0.009$ for TG; $r= -0.086$, $p<0.035$ for HDL; $r=0.025$, $p<0.001$ for LDL-chol). In females TC, TG and LDL-chol levels correlated significantly with HbA1c ($r=0.124$, $p<0.002$ for TC; $r=0.115$, $p<0.003$ for TG; $r=0.116$, $p<0.003$ for LDL-chol) whereas HDL-chol did not.

Table II shows lipid parameters categorized by patients' glycemic control. Table III and IV show the comparison of lipid profiles among different groups (based on HbA1c%) of male and female subjects. We found significant difference in all the parameters of lipid profile among different groups in males ($p<0.001$ for TC, $p=0.006$ for TG, $p=0.023$ for HDL-chol and $p<0.001$ for LDL-chol). TC, TG and LDL-chol increased from Group A to Group C indicating gradual increase of these parameters with increase in HbA1c% whereas HDL-chol decreased from Group A to Group B with no further decrease with increase in HbA1c%.

Table I: Mean age, HbA1c and circulating blood lipids of study subjects

Variables	Total (n=1253)	Male (n=610)	Female (n=643)	p values
Mean age (years)	50.35 ± 11.65	51 ± 12	50 ± 12	0.287
Mean HbA1c (%)	9.24 ± 2.43	9.3 ± 2.4	9.2 ± 2.4	0.514
TC (mg/dL)	184.29 ± 42.31	179 ± 41	189 ± 43	<0.001
TG (mg/dL)	175.35 ± 75.11	178 ± 75	173 ± 75	0.238
HDL-chol (mg/dL)	38.72 ± 8.33	36 ± 7	41 ± 9	<0.001
LDL-chol (mg/dL)	110.39 ± 37.02	107 ± 36	113 ± 37	0.004

p values were achieved by Unpaired Student's *t* test. p values for male vs female

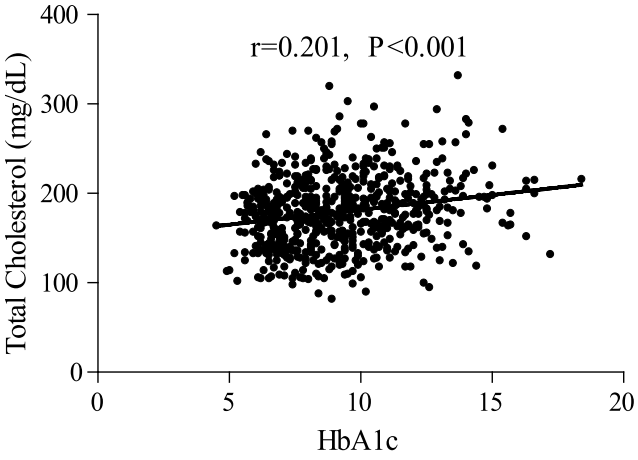

Fig 1a. Correlation of TC with HbA1c% in males

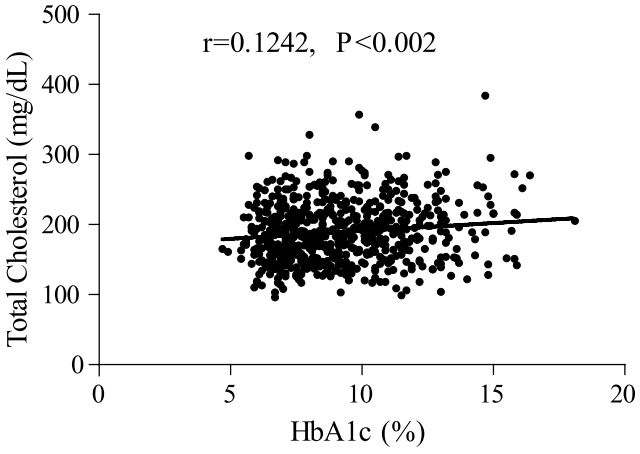

Fig 1b. Correlation of TC with HbA1c% in females

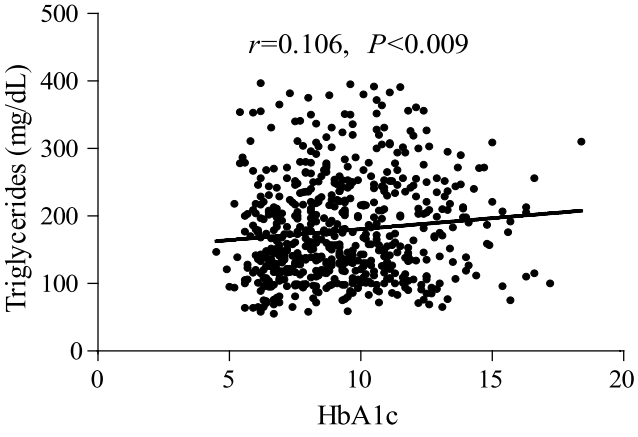

Fig 2a. Correlation of TG with HbA1c% in males

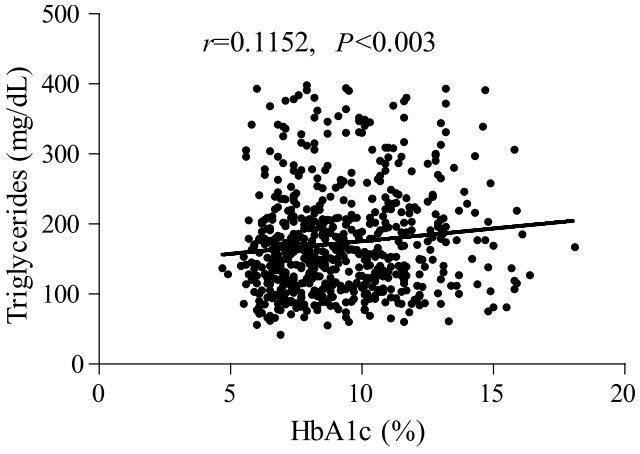

Fig 2b. Correlation of TG with HbA1c% in females

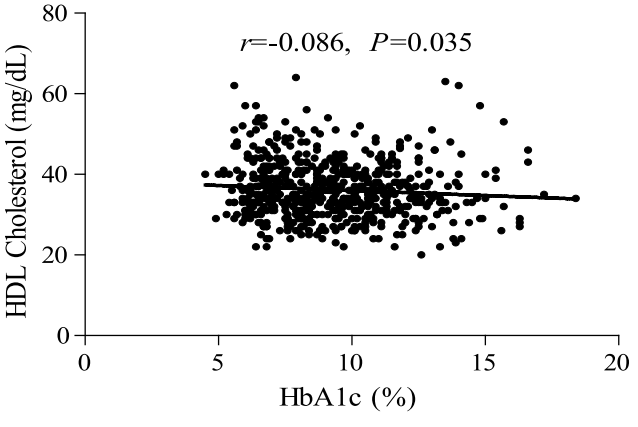

Fig 3a. Correlation of HDL-chol with HbA1c% in males

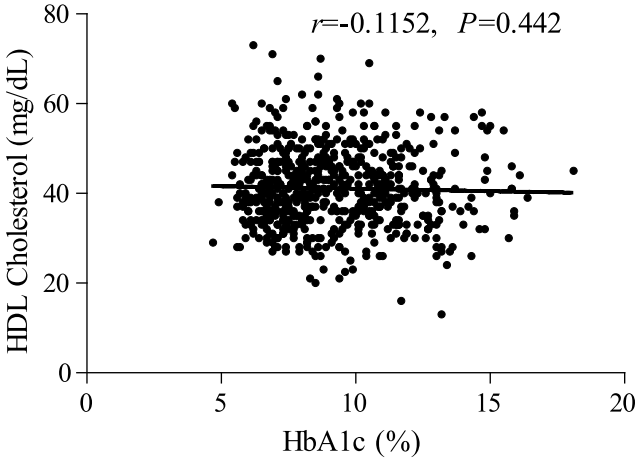

Fig 3b. Correlation of HDL-chol with HbA1c% in females

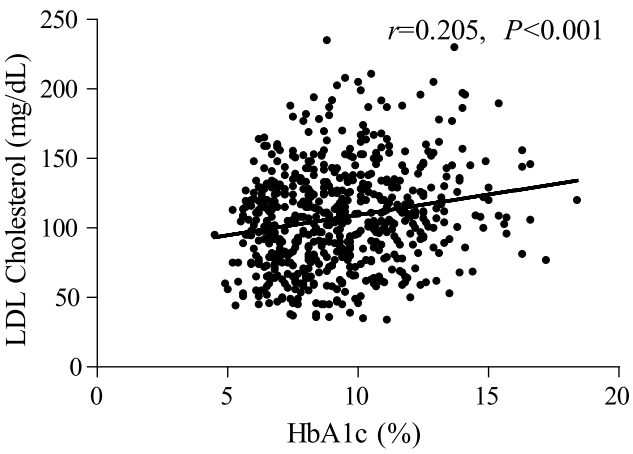

Fig 4a. Correlation of LDL-chol with HbA1c% in males

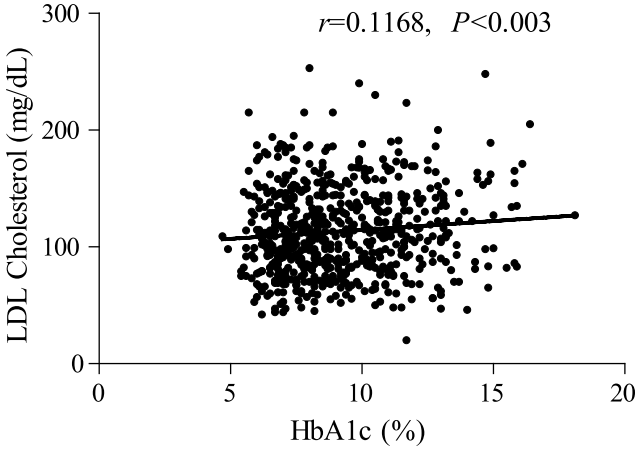

Fig 4b. Correlation of LDL-chol with HbA1c% in females

Table II: Lipid parameters categorized by patients' glycemic control (Hb A1c)

Parameters	Group A (n=249)	Group B (n=568)	Group C (n=436)	p values
HbA1c (%)	6.3 ± 0.5	8.4 ± 0.9	12.0 ± 1.6	A vs B: <0.001 B vs C: <0.001 A vs C: <0.001
TC (mg/dL)	176 ± 38	182 ± 43	192 ± 43	A vs B: 0.029 B vs C: <0.001 A vs C: <0.001
TG (mg/dL)	158 ± 70	176 ± 74	184 ± 78	A vs B: <0.001 B vs C: 0.106 A vs C: <0.001
HDL-chol (mg/dL)	39 ± 8	39 ± 8	38 ± 8	A vs B: 0.451 B vs C: 0.153 A vs C: 0.064
LDL-chol (mg/dL)	105 ± 34	108 ± 38	117 ± 37	A vs B: 0.219 B vs C: <0.001 A vs C: <0.001

Group A, HbA1c<7%; Group B, (HbA1c: 7-10%; Group C, Hb A1c>10%

Table III: Lipid profile in different groups of male subjects (n=610)

Parameters	Group A (n=125)	Group B (n=271)	Group C (n=214)	p values
Total cholesterol (mg/dL)	170 ± 33	176 ± 42	189 ± 41	<0.001
Triglycerides (mg/dL)	161 ± 73	178 ± 71	188 ± 79	0.006
HDL-cholesterol (mg/dL)	38 ± 8	36 ± 7	36 ± 7	0.023
LDL-cholesterol (mg/dL)	107 ± 26	111 ± 32	122 ± 31	<0.001

Group A, HbA1c<7%; Group B, (HbA1c: 7-10%; Group C, Hb A1c>10% p values are generated by one way ANOVA

Table IV: Lipid profile in different groups of female subjects (n=643)

Parameters	Group A (n=124)	Group B (n=297)	Group C (n=222)	p values
Total cholesterol (mg/dL)	181 ± 43	189 ± 43	194 ± 45	0.030
Triglycerides (mg/dL)	155 ± 67	174 ± 67	180 ± 77	0.006
HDL-cholesterol (mg/dL)	41 ± 9	42 ± 9	41 ± 9	0.373
LDL-cholesterol (mg/dL)	115 ± 31	119 ± 32	123 ± 33	0.078

Group A, HbA1c<7%; Group B, (HbA1c: 7-10%; Group C, Hb A1c>10% p values are generated by one way ANOVA

In female subjects, we found significant difference in TC and TG among different groups, but not in HDL-chol and LDL-chol values (p=0.030 for TC, p=0.006 for TG, p=0.373 for HDL-chol and p=0.078 for LDL-chol). The two parameters TC and TG increased from Group A to Group C indicating gradual increase of these parameters with increase in HbA1c%. Regarding LDL-chol we found apparently gradual increase from Group A to Group C with increase in HbA1c. Here we observed a positive trend for LDL-chol to increase with increase in HbA1c%. This trend for LDL-chol is significant (p=0.027).

Multiple linear regression analysis considering HbA1c as dependent variable and TC, TG and HDL-chol as independent variables showed that HbA1c is significantly and positively associated with TC (β = 0.183, p<0.001) and inversely associated with HDL-chol (β= −0.108, p<0.001). When adjusted to sex, this association retains its significance (β=0.183, p<0.001 for TC and β= −0.016, p= 0.001 for HDL-chol).

Discussion

In this study we found that TC and TG increased significantly in males and females with increase in HbA1c%. In males LDL-chol also increased significantly keeping pace with HbA1c. HDL-chol decreased in Group B and C compared with Group A. In females, LDL-chol apparently increased with increase in HbA1c, but it was not statistically significant (p=0.078). We also found that increase in TC, TG and LDL-chol and decrease in HDL-chol in males and increase in TC, TG and LDL-chol in females correlated significantly with increase in HbA1c. Decrease in HDL-chol in females did not correlate significantly.

Multiple linear regression analysis showed that HbA1c was positively associated with TC and negatively associated with HDL-chol after adjustment of sex.

In another study direct and significant correlation of HbA1c with serum TC, TG and LDL-chol and inverse correlation with HDL-chol were found. In this study there was a linear significant increase in TC, TG and LDL-chol in patients of both genders with impaired glycemic control. Serum HDL-chol showed a significant and inverse relationship with uncontrolled hyperglycemia in females but not in males. The findings of this study suggest that HbA1c can provide valuable supplementary information about the extent of circulating lipids besides its rules in monitoring

long-term glycemic control.[14] This study is also in consistence with ours one for TC, TG and LDL-chol but not for HDL-chol. In our study, HDL cholesterol showed negative correlation with HbA1c in male but not in female. This difference in case of HDL cholesterol between two studies may be because of biological variation in different population, and it can be further explored by more studies in different settings.

In a nation-wide multicentered survey involving 1275 type 1 diabetic subjects and 171 normal controls in Brazil, Giuffrida et al[19] found heterogenous behavior of lipids according to HbA1c which is not consistent with our findings. In their study TG and LDL-chol worsened alongside HbA1c. They found consistent association of lower HDL-chol with higher daily insulin dose.

Li et al[20] conducted a study involving 95 lipid loci and tested their association collectively and individually with fasting plasma glucose (FPG), HbA1c and insulin resistance in two independent cohorts of 10,995 and 2438 subjects. Their findings suggest a complex genetic regulation and metabolic interplay between lipids and glucose.

A study done by Khan et al[21] examined the impact of glycemic control on the lipid profile of diabetic patients and also determined the ability of HbA1c as an indirect marker of dyslipidaemia. They found that there is a linear relationship between HbA1c and dyslipidaemia and concluded that HbA1c is not only a useful biomarker of long-term glycemic control but also a good predictor of lipid profile.[21] But another study done by Mete et al[22] revealed that while the intensity of the lipid and BP control was not correlated with glycemia control, baseline HbA1c correlated with lesser reductions in systolic blood pressure, LDL-chol, and non-HDL-chol and lower chances of achieving the targets for these measures. They concluded that although carotid atherosclerosis was significantly related to baseline HbA1c, degree of glycemia did not influence the effects of lipid and BP lowering on carotid atherosclerosis. Another study done by Davidson et al[23] found that for patients with diabetes mellitus and elevated TG, the effect of HbA1c reduction has limited effects on TG reduction.

From the findings of our study we can conclude that TC, TG and LDL-chol increase with increasing HbA1c with positive correlation in both males and females; but there is no significant correlation between HDL-chol levels and HbA1c in females as significant negative correlation between HDL-chol and HbA1c was found only in males. The findings of this study also suggest that HbA1c is not only a useful biomarker of long-time glycemic control, but also a good marker of relative increase of serum TC, TG and LDL-chol. But the use of HbA1c as a marker of lipid status should be used with cautions as the relationship of HbA1c and blood lipids found in different studies are not consistent. However, we recommend more comprehensive studies in different settings.

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