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Association between glycaemic control and serum lipids profile in type 2 diabetic patients: HbA_{1c} predicts dyslipidaemia

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Abstract Impaired lipid metabolism resulting from uncontrolled hyperglycaemia has been implicated in cardiovascular complications in diabetes patients. The aim of this study was to examine the impact of glycaemic control on the lipid profile of diabetic patients. We also determined the ability of glycated haemoglobin (HbA_{1c}) as an indirect marker of dyslipidaemia. A total of 1011 type 2 diabetic patients (males, 574; females, 437; mean age, 59.76 years) were included in this study. Venous blood samples were collected from all the subjects after at least 8 h fasting. The sera were analysed for HbA_{1c}, fasting blood glucose (FBG), total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL). The levels of HbA_{1c}, FBG and LDL did not differ significantly between males and females. Female patients showed significantly higher serum cholesterol and HDL but significantly lower TG levels as compared to males. There was a highly significant correlation between HbA_{1c} and FBG. Both HbA_{1c} and FBG exhibited direct correlations with cholesterol, TG and LDL and inverse correlation with HDL; the magnitude of significance for all these lipid parameters being greater with HbA_{1c} than FBG. There was a linear relationship between HbA_{1c} and dyslipidaemia. The levels of serum cholesterol and TG were significantly higher and of HDL significantly lower in patients with worse glycaemic control as compared to patients with good glycaemic control. The findings of this study clearly indicate that HbA_{1c} is not only a useful biomarker of long-term glycaemic control but also a good predictor of lipid profile. Thus, monitoring of glycaemic control using HbA_{1c} could have additional benefits of identifying diabetic patients who are at a greater risk of cardiovascular complications.

Key words Diabetes • Cardiovascular disease • HbA_{1c} • Lipid profile • Biomarker

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Introduction

Besides enduring multiple complications of chronic hyperglycaemia, diabetic patients tend to be soft targets of deadly cardiovascular disease (CVD). The major cause of the reduction in life expectancy in diabetic patients is associated with cardiovascular complications [1, 2]. Quantitatively, subjects with diabetes have more than two-fold increased risk for cardiovascular death compared with persons without diabetes [3, 4]. The synchronous occurrence of diabetes and cardiovascular events is evident from the findings of a cohort of acute coronary syndrome patients (without prior glycaemic checkout) showing that few patients (16.4%) had normal glucose tolerance and the remaining were either diabetic or had impaired glucose tolerance [5]. Furthermore, the role of hyperglycaemia in CVD is supported by a direct correla-

tion between fasting blood glucose (FBG) and cardiovascular events [6, 7]. Even isolated postprandial hyperglycaemia has been suggested to be a cardiovascular risk factor [8]. It has been noticed that glucose fluctuations (glucose swing) during postprandial periods exhibit a more specific triggering effect on oxidative stress than chronic hyperglycaemia [9].

Glycated haemoglobin (HbA_{1c}) is an important indicator of long-term glycaemic control with the ability to reflect the cumulative glycaemic history of the preceding 2–3 months. Recently, elevated HbA_{1c} has been regarded as an independent risk factor for coronary heart disease (CHD) [10] and stroke [11] in subjects with or without diabetes. Ravipati et al. [12] observed a direct correlation between HbA_{1c} and the severity of coronary artery disease in diabetic patients. The impact of poor glycaemic control is so grave that increased maternal HbA_{1c} could impair foetal long axis cardiac function [13], whereas improving glycaemic control can substantially reduce the risk of cardiovascular events in diabetics [14, 15]. It has been estimated that reducing the HbA_{1c} level by 0.2% could lower the mortality by 10% [16]. Vaag [17] has suggested that improving glycaemic control in patients with type 2 diabetes may be more important than treating dyslipidaemia for the prevention of both microvascular and macrovascular complications.

Patients with type 2 diabetes often exhibit an atherogenic lipid profile (high TG and low HDL cholesterol) which greatly increases their risk of CVD compared with people without diabetes [18]. Recently, patients with type 2 diabetes carrying apolipoprotein E 4 genotype were found to have a greater cardiovascular risk owing to metabolic variation in lipid metabolism leading to higher cholesterol and LDL [19]. Giansanti et al. [20] also observed significantly higher levels of hypercholesterolaemia and hyperlipidaemia in type 2 diabetic patients with CVD as compared to diabetic patients without CVD. Interestingly, attempts to reduce cardiovascular risks resulted in the improvement of HbA_{1c} even in the absence of any specific intervention targeted at improving glycaemic control [21]. The above findings clearly indicate the clinical significance of complex interactions involved in the integration of carbohydrate and lipid metabolism. The aim of this study was to examine the effect of glycaemic control (using HbA_{1c} as biomarker) on the lipid profile of type 2 diabetic patients. We also investigated whether the extent of dyslipidaemia can be indirectly evaluated on the basis of specific cut-off values of HbA_{1c}.

Patients and methods

A total of 1011 type 2 diabetic patients (574 males and 437 females) visiting the clinics of Armed Forces Hospital, Riyadh were included in this study. The mean age±standard deviation of male and female subjects was 62.72±10.24 and 55.86±12.08 years respectively. Venous blood samples were collected in serum separator vacutainers from all the subjects after at least 8 h fasting. The sera were analysed for HbA_{1c}, FBG, total cholesterol, triglycerides (TG) and high-density lipoprotein cholesterol (HDL) using an autoanalyser (Roche Modular P-800, Germany). The level of low-density lipoprotein cholesterol (LDL) was determined using the formula: LDL=(cholesterol–TG)/(2.2–HDL).

The data were evaluated by SPSS statistical package version 10. Pearson's correlation test was performed to examine various correlations. Independent samples Student's *t*-test (2-tailed) was used to compare means of different parameters between males and females. The effect of glycaemic control on various parameters was evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. P values ≤0.05 were considered as statistically significant.

Results

The levels of HbA_{1c} and FBG did not differ significantly between males and females (Table 1). There was a highly significant correlation between HbA_{1c} and FBG (R^2=0.685, P=0.000) (Fig. 1). The age of patients did not show any significant correlation with either HbA_{1c}

Table 1 Serum biochemistry of male and female type 2 diabetes patients

Parameter	Males (n=574)			Females (n=437)			P
	Mean	SD	Range	Mean	SD	Range	
HbA_{1c}	8.064	2.207	4.43–19.58	8.161	2.348	4.53–15.94	0.500
FBG	9.161	3.780	2.60–27.60	9.183	4.072	3.40–33.40	0.937
Cholesterol	5.021	1.077	2.16–9.20	5.212	1.112	2.56–9.81	0.007*
Triglycerides	2.052	1.226	0.52–11.14	1.815	1.083	0.48–11.56	0.002*
HDL	1.104	0.288	0.37–2.71	1.361	0.336	0.55–3.27	0.000*
LDL	3.107	1.059	0.93–7.00	3.280	1.095	0.65–7.31	0.057

*Statistically significant; males *vs*. females

(R^2=0.005, P=0.877) or FBG (R^2=0.064, P=0.068). Although there was no significant difference in LDL levels between males and females, the levels of cholesterol and HDL were significantly higher and TG significantly lower in females as compared to male type 2 diabetic patients (Table 1). Both HbA_{1c} and FBG exhibited direct correlations with cholesterol, TG and LDL and an inverse correlation with HDL; all these correlations were significant except FBG *vs*. HDL (Table 2). The magnitude of correlation between lipid profile and HbA_{1c} was much greater than its correlation with FBG. The age of the patients was significantly and inversely correlated with cholesterol, HDL and LDL, whereas it was not correlated with TG (Table 2).

The impact of glycaemic control on various parameters was evaluated by categorising all the patients into 3 groups on the basis of HbA_{1c} levels: group 1, good glycaemic control (HbA_{1c}≤6%); group 2, poor glycaemic control (HbA_{1c} >6%–9%) and group 3, worst glycaemic control (HbA_{1c}>9%). The concentration of FBG was significantly higher (ANOVA F=252.43, P=0.000) in group 3 (mean±SEM, 12.497±0.266 mmol/l) and group 2 (8.166±0.124 mmol/l) than group 1 (5.895±0.098 mmol/l) (Fig. 2a). The level of cholesterol was significantly higher (ANOVA F=3.807, P=0.023) in group 3 (5.249±0.067 mmol/l) as compared to group 2 (5.029±0.048 mmol/l) (Fig. 2b). The patients in group 3 (2.137±0.071 mmol/l) and group 2 (1.918±0.053 mmol/l) had significantly higher TG levels as compared to group 1 (1.710±0.065 mmol/l) (ANOVA F=7.447, P=0.001, Fig. 2c). There was a significant decrease in HDL levels in group 3 patients (1.146±0.021 mmol/l) as compared to group 1 (1.288±0.034 mmol/l) and group 2 (1.232±0.019 mmol/l) patients (ANOVA F=6.851, P=0.001, Fig. 2d). No significant differences were observed with regard to glycaemic control and LDL (ANOVA F=2.763, P=0.064, Fig. 2e) or patients' age (ANOVA F=2.312, P=0.100, Fig. 2f).

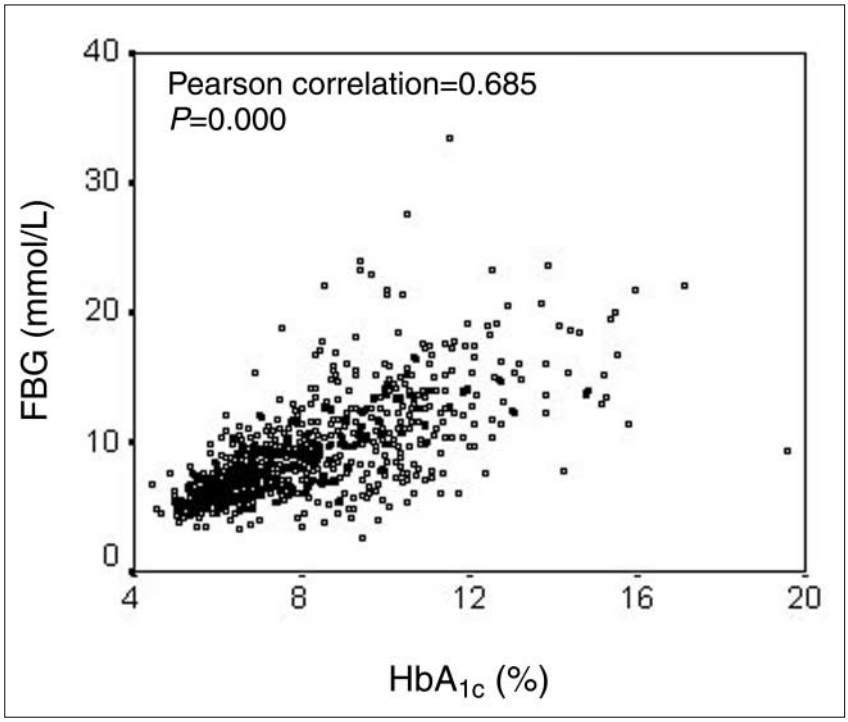

Fig. 1 Correlation between HbA_{1c} and FBG in type 2 diabetic patients

Table 2 Correlations between lipid profiles and HbA_{1c}, FBG and age of type 2 diabetic patients

Parameters	HbA_{1c}		FBG		Age	
	Pearson correlation	P	Pearson correlation	P	Pearson correlation	P
Cholesterol	0.127	0.000*	0.086	0.015*	–0.099	0.002*
Triglycerides	0.153	0.000*	0.134	0.000*	0.028	0.379
HDL	–0.128	0.002*	–0.078	0.080	–0.080	0.050*
LDL	0.142	0.001*	0.121	0.007*	–0.121	0.004*

*Statistically significant

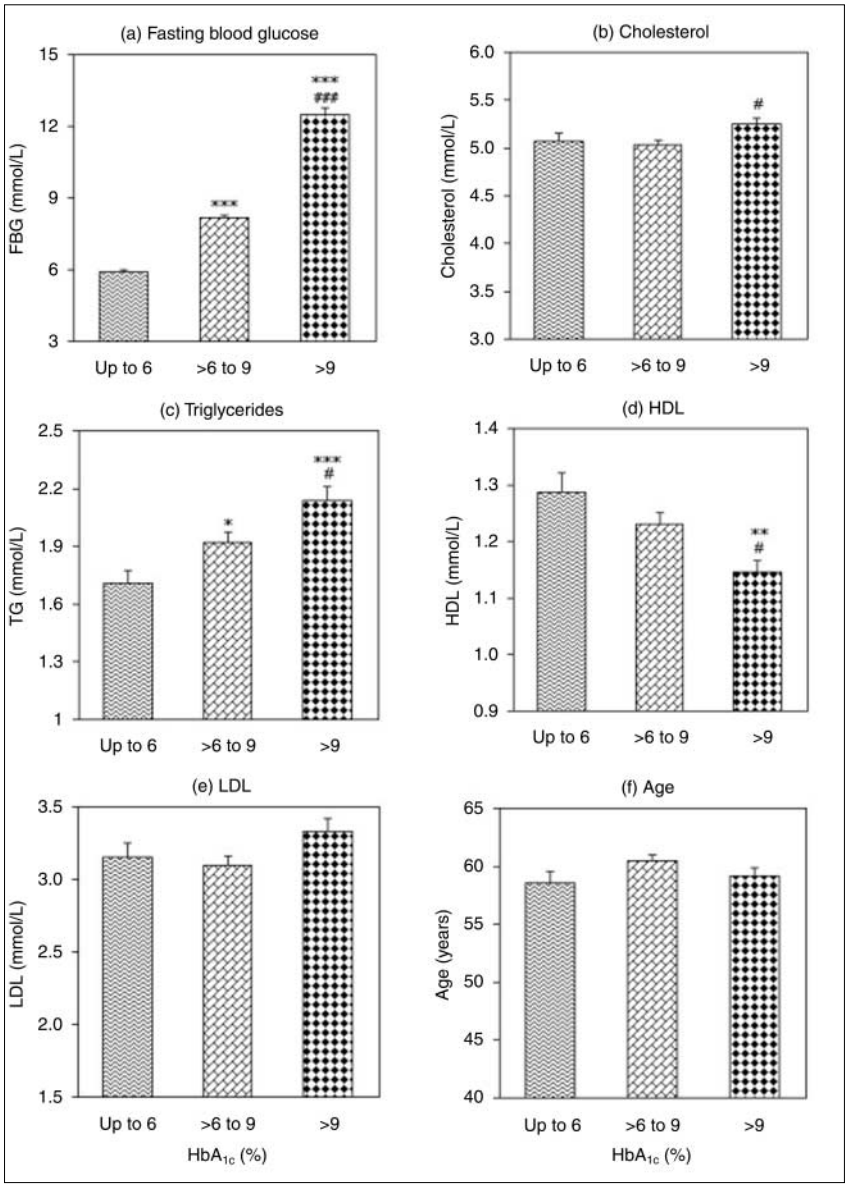

Fig. 2 Impact of glycaemic control on various parameters. All the patients were categorised into 3 groups according to their HbA_{1c} levels: group 1 ($HbA_{1c} \leq 6\%$), group 2 (HbA_{1c} >6%–9%) and group 3 (HbA_{1c} >9%). **P*<0.05, ***P*<0.01 and ****P*<0.001 group 1 versus group 2; #*P*<0.05 and ###*P*<0.001 group 2 *vs*. group 3

Discussion

The significant correlation between HbA_{1c} and FBG (Fig. 1) is in agreement with earlier reports [22–24] as to the absence of a significant correlation between HbA_{1c} and age [25]. The results of this study clearly showed that the levels of HbA_{1c} and FBG are not affected by patients' gender as neither of these parameters differed significantly between male and female diabetic patients (Table 1). Earlier, it was noticed that type 2 diabetic patients without CHD had the same HbA_{1c} levels irrespective of gender whereas female patients with CHD had higher HbA_{1c} than respective male controls [26]. Diabetes confers a markedly increased risk of CHD events in both women and men [27]. However, women with diabetes appear to have experienced an increased CHD mortality [28]. Diabetic women may be subject to more adverse changes in coagulation, vascular function and CHD risk factors than diabetic men [29–31]. In this study, female patients had significantly higher levels of cholesterol and HDL than males; LDL being similar in both the sexes (Table 1). Similar differences in lipid profiles of male and female diabetic patients have been reported earlier [26, 32–34]. It is important to note that diabetic patients continued to be at increased risk of CHD if their HDL levels remain suboptimal despite successful reductions of LDL with statin therapy [18]. However, susceptibility to CVD among type 2 diabetic patients differs markedly according to ethnicity and gender [35], though converse findings also exist [36].

We observed significant correlations between HbA_{1c} and cholesterol, TG, HDL and LDL in diabetic patients (Table 2), which is in agreement with the findings of sev-

eral other investigators who reported significant correlations between HbA_{1c} and lipid profiles and suggested the importance of good management of diabetes in controlling dyslipidaemia [23, 37–39]. The comparatively stronger association of HbA_{1c} than FBG with lipid profile is supported by an earlier study reporting higher correlation coefficients for HbA_{1c} than random glucose *vs*. cholesterol, TG and LDL [40]. Although both FBG and HbA_{1c} have been related to CHD in a similar fashion, the former association has been found to be much weaker [10].

The diabetic patients with poor glycaemic control exhibited a significant increase in cholesterol and TG and a decrease in HDL without any significant alteration in LDL (Fig. 2). The magnitude of impaired glycaemic control as defined by 3 different cutoff values of HbA_{1c} was proportionally related with dyslipidaemia in terms of significantly higher cholesterol and TG and lower HDL levels (Fig. 2). The arbitrary cutoff values of HbA_{1c} used by us are based on earlier studies. Selvin et al. [14] defined good and poor glycaemic control on the basis of HbA_{1c}<6.0% and >7.5% respectively, whereas other investigators used the levels of HbA_{1c}<7.0% and >7.0% as indicators of good and poor glycaemic control respectively [24, 41]. On the other hand, Akbar et al. [36] relied on a much higher cutoff value of HbA_{1c} (>9.0%) as a predictor of poor glycaemic control. Selvin et al. [10] have demonstrated a linear relationship between CHD and HbA_{1c} in diabetic patients, suggesting that the risk of CHD begins to increase at HbA_{1c} levels even below 7.0%. Grant et al. [40] have reported significantly higher CVD risk factors among individuals with HbA_{1c}>6.0%.

It has been reported that HDL cholesterol is inversely and non-HDL cholesterol directly associated with CHD risk in diabetes patients [42]. Another study on female type 2 diabetic patients has revealed that association between non-HDL cholesterol and CHD risk is apparent in patients with elevated TG [43]. Moreover, significantly high serum TG levels have been found in diabetic patients with CHD as compared to non-diabetic patients [34]. Onat et al. [44] have suggested that fasting TG levels are predictive for future CVD independent of age, diabetes, total cholesterol and HDL. The above discussion clearly indicates the clinical significance of various lipid parameters including total cholesterol, TG, HDL and LDL in predisposing diabetic patients to cardiovascular complications. The significant correlation of HbA_{1c} with all these lipid parameters (Table 2) points towards the usefulness of HbA_{1c} for screening high-risk diabetic patients.

In conclusion, the findings of this study clearly show that HbA_{1c} is not only a reliable biomarker of glycaemic control but also a good predictor of serum lipid profile in diabetic patients. Diabetic patients with HbA_{1c} >6%–9% and >9% tend to have moderate and severe dyslipidaemia respectively and therefore should be examined thoroughly for their lipid profile and associated complications.

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