EUROMEDITERRANEAN BIOMEDICAL JOURNAL

for young doctors

Original article

GLYCAEMIC CONTROL PROFILE IN DIABETIC PATIENTS: A SUB-ANALYSIS OF THE PHOENIX LIFESTYLE PROJECT

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Summary

Diabetes Mellitus is regarded as an independent risk factor for cardiovascular disease and is highly prevalent in the Asian Indian community in South Africa. Poor control of blood glucose is associated with an increased risk for coronary artery disease (CAD). We determined the glycaemic control profile in a sample of known diabetic subjects from the Phoenix Lifestyle project cohort, and examined the relationship between glycaemic control and other biochemical parameters.

This is the first study in the Asian Indian community in Phoenix that determined the relationship between glycaemic control in diabetic subjects and other cardiovascular risk factors. Our study shows that significant dyslipidemia is present in the majority of diabetics with poor glycemic control, as well as in subjects with HBA1c levels demonstrative of good control. Atherogenic dyslipidemia in diabetic subjects is a substrate for the premature development of CAD in diabetes.

Introduction

The marked increase in the prevalence of cardiovascular (CV) risk factors, such as glucose and lipid abnormalities, is fueling the current epidemic of diabetes mellitus (DM) in both developed and developing countries[1]. Asian Indians are known to have a high propensity for the development of DM across the diaspora[2, 3]. The prevalence of diabetes in South African Asian Indians has been documented to be around 15-18%[4, 5, 6] and is perceived to be the explanation for the high prevalence of coronary artery disease (CAD) in this ethnic group[7].

Diabetes is regarded as an independent risk factor for cardiovascular disease (CVD)[8]. Impaired insulin secretion and insulin resistance in diabetes account for the majority of the biochemical changes seen in diabetes. Chronic hyperglycemia and the alterations in lipid profile all contribute to the development of atherosclerosis[9].Haemoglobin

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Received: *29th January, 2016 — **Revised:** 18th February, 2016 — **Accepted:** 29th March, 2016*

A1c (HbA1c) provides an estimate of glycemic control in the preceding two to three months[10], and is a strong predictor for the development of micro- and macrovascular disease[11], even in non-diabetic subjects[12]. HbA1c is formed when glucose reacts non-enzymatically with the NH2-terminal amino acid of the beta chain of human haemoglobin by a ketoamine linkage, forming slowly over the 120-day lifespan of the erythrocyte[13]. In this study we examined the relationship between glycaemic control (as assessed by the HbA1c)and other biochemical parameters.

Materials and method

The Phoenix Lifestyle Project was an analytical and cross-sectional study that examined cardiovascular risk factors in 1,490 randomly selected subjects in the Cadastral district of Phoenix, north of Durban. Detailed methodology has previously been described [14]. After informed consent was obtained, blood samples were collected after overnight fasting to procure biochemistry measurements of plasma glucose, serum insulin and serum lipids (total cholesterol, HDL-cholesterol, and total triglycerides). LDL was calculated using the Friedwald equation, fasting blood glucose was measured using the Glucose oxidase method, and plasma insulin was measured by immunoassay.

In this analysis, we selected all of the participants from the Phoenix Lifestyle project who were diagnosed with diabetes. Diabetes was diagnosed when subjects self-reported the condition or were on medication for glycaemic control. Additionally, the American Diabetes Association criteria[15]was used for classifying glycaemic categories based on fasting plasma glucose (FPG): diabetes diagnosis if FPG ≥ 7.0mmol/l or oral glucose tolerance test (OGTT) ≥ 11.0 mmol/l. Glycaemic control was based on the criteria used by Khan et al[16]: group 1 (good glycaemic control: HbA1c≤6%); group 2 (poorly controlled: HbA1c>6- ≤9%) and group 3 (uncontrolled: HbA1c>9%). Diabetic dyslipidaemia was diagnosed if subjects had the concomitant presence of raised levels of LDL and triglycerides, as well as reduced levels of HDL.

Statistical analysis

Statistical analysis was performed using the SPSS statistical package (version 23.0). All data was described as means and SD. The independent sample T-test was used to compare data between men and women in order to ascertain statistically significant differences: a p-value < 0.05 was considered statistically significant. Pearson's correlation was performed in order to determine the strength of association between biochemical parameters and age, HbA1c and fasting blood glucose. One-way analysis of variance (ANOVA) was used to determine the effect of glycaemic control on biochemical parameters.

Ethical considerations

This study received full ethical clearance from the University of KwaZulu-Natal ethics committee (BREC) (BE 172/09).

Results

Of the 1,490 subjects that were recruited, complete data was available for 1,374 subjects. Diabetes was diagnosed, as indicated above, in 431 subjects, a prevalence of 32%[14] without age distinctions. There was a predominance of women (339/78.7%). The demographic and biochemical data is shown in Table 1. The biochemistry revealed elevated levels of triglycerides and total serum cholesterol, and low levels of HDL. Glycaemic control was poor (HbA1c = 8.8 ±2.3%). Aside from HDL (p=0.002), for which there were gender differences in the normal ranges, there were no other significant differences for biochemical parame-

ters between men and women. We then examined the effect of age on biochemistry and found that increasing age was significantly associated with elevation in total cholesterol levels (R^2 = 0.128; p=0.008) and serum triglycerides (R^2 = 0.107; p=0.027) (Table 2). We also looked at the level of glycemic control, as assessed by HbA1c, and fasting blood glucose on the biochemical parameters tested. The fasting blood glucose correlated with all biochemical parameters, the strongest being with LDL cholesterol (R^2 = 0.818; p<0.001). In keeping with the effect of diabetes, there was a significant negative correlation between fasting blood glucose and HDL (R^2 = -0.28 p<0.001). Interestingly, this association was not present between HbA1c and HDL cholesterol.

We then established the biochemical profile in each of the categories of glycemic control to determine the effects of worsening control on the biochemistry. The majority of subjects (391/90.7%) were classified with poor or uncontrolled glycaemia (HbA1c > 9.0%): there was no significant difference in the ages of subjects within each of the groups, nor was there a significant difference in the concentrations of total serum cholesterol, HDL or LDL (Table 3). However, the blood glucose and triglyceride levels were significantly higher (p<0.001) in group 3

Parameter	All (n=431)	Men (n=92)	Women (n=339)	P value*
Age	50±9	52±9	50±9	0.577
FBG(mmol/l)	9.1±3.6	9.1±3.2	9.1±3.7	0.152
Tc(mmol/l)	5.7±1.2	5.7±1.2	5.8±1.2	0.106
Tg(mmol/l)	2.2±1.3	2.5±1.6	2.1±1.2	0.130
HDL(mmol/l)	1.25±0.30	1.17±0.36	1.28±0.27	**0.002**
LDL (mmol/l)	3.47±1.07	3.35±1.06	3.5±1.07	0.197
HbA1c(%)	8.8±2.3	8.6±2.1	8.9±2.4	0.770
Diabetic dyslipidaemia	61(14.2%)	25(27.1)	36(10.6%)	**<0.001**
FBG: fasting blood glucose; Tc: total serum cholesterol; Tg: triglycerides				

Table 1. Demographic and biochemical data

	Age		HbA1c		FBG	
Parameters	Pearson's correlation	p	Pearson's correlation	p	Pearson's correlation	p
FBG(mmol/l)	-0.04	0.935	0.598	**<0.001**		
TC(mmol/l)	0.128	**0.008**	0.118	**0.014**	0.158	**0.001**
Tg(mmol/l)	0.107	**0.027**	0.132	**0.006**	0.161	**0.001**
HDL(mmol/l)	0.044	0.365	-0.044	0.361	-0.280	**<0.001**
LDL	0.025	0.619	0.124	**0.013**	0.818	**<0.001**
HbA1c (%)	0.018	0.703			0.598	**<0.001**
FBG: fasting blood glucose; Tc: total serum cholesterol; Tg: triglycerides						

Table 2. Correlations between biochemical parameters and Age, HBA1C and fasting blood glucose

(uncontrolled group) with respect to group 1 (good glycaemic control group). Diabetic dyslipidaemia was found in 14.2% of subjects and was significantly higher in men (p< 0.001).

Discussion

The high prevalence of diabetes amongst Asian Indians in the Phoenix community is associated with poor or uncontrolled glycaemia, and invariably accompanied by diabetic dyslipidaemia (14.2%). All lipid parameters were abnormal. The mechanism underlying these abnormalities has been attributed to Insulin resistance (IR). Insulin resistance causes defects in LDL clearance, leading to raised LDL levels[17]. In addition, the composition of this LDL is altered to form small, dense, triglyceride-enriched LDL, which is easily oxidized, engulfed by macrophages to form foam cells, thus playing a major role in the pathogenesis of atherosclerosis[8]. Increased numbers of triglycerides are caused by the overproduction and defective clearance of VLDL triglycerides, decreased lipoprotein lipase activity or decreased production of lipoprotein B[17]. Hyperglycaemia, with concomitant low levels of HDL, is caused by increased levels of hepatic lipase with subsequent increased clearance of HDL. Impaired VLDL catabolism further results in decreased formation of HDL[18]. Our subjects presented with increased levels of LDL, triglycerides, and total serum cholesterol, as well as low HDL levels. This is characteristic of diabetic dyslipidaemia (raised LDL and triglyceride levels and low HDL).

The interaction of hyperglycemia and dyslipidemia further increases the risk for the development of macro and microvascular complications[19], which is thought to occur due to endothelial damage from hyperglycemia-induced overproduction of superoxide [20]. The high free fatty acid (FFA) levels induce insulin resistance, causing increased production of superoxide in arterial endothelial cells, activating proinflammatory signals and leads to impaired endothelial function. These metabolic changes explain the increasing prevalence of premature CAD, which has been found in our Asian Indian community[7].

Overall, our subjects presented with poor glycaemic control (HbA1c>6 %-< 9%) with the vast majority of them (43.9%) being classified as uncontrolled glycaemia (Hb> 9%). HbA1c rises in the presence of DM due to the substantially higher proportion of haemoglobin that is glycosolated[13].There were statistically significant correlations between HbA1c and total cholesterol, triglyceride and LDL levels (p<0.05).This is similar to other stud-

	Group 1 (good) n=40 (9.2%)	Group 2 (poor) n= 202 (46.7%)	Group 3 (uncontrolled) n=189 (43.9%)	p-value*
Age (years)	48	51	50	0.567
FBG(mmol/l)	6.7	7.1	11.7	**<0.001**
Tc(mmol/l)	5.5	5.7	5.9	0.087
Tg(mmol/l)	1.8	2.2	2.4	**0.015**
HDL (mmol/l)	1.32	1.25	1.25	0.999
LDL	3.24	3.39	3.62	0.085
**values for Group 1 versus Group 3 have been shown* *FBG: fasting blood glucose; Tc: total serum cholesterol; Tg: triglycerides*				

Table 3. Biochemical profile in relation to HbA1c categories

ies where a positive correlation was shown between HbA1c and lipid parameters[16, 21,22]. The mean biochemical parameters for men and women in our study were similarly elevated. As expected, HDL levels were significantly higher in women (p = 0.02), similar to that of other documented studies [22, 23]. The higher HDL is thought to be due to the effects of sex hormones on body fat distribution, leading to differences in lipoprotein levels[24].

Of note, total serum cholesterol, HDL, and LDL levels were similarly elevated in all three groups, and in contrast to other studies, this dyslipidaemia pattern was present even in subjects with well-controlled glycaemic profiles. This may be due to the effect of insulin resistance or pre-diabetes, which is thought to impair the mechanism that suppresses fatty acid release from adipose tissue after food intake [20, 25].

Diabetes mellitus is an independent risk factor for CAD, and by virtue of this, is associated with the same near-term risk for a coronary event as compared to a patient with existing CAD[26]. Elevated HbA1c is associated with increased mortality, and each percentage point increase in HbA1c is associated with a 35% increase in the risk for macrovascular complications and an 18% increase in risk of myocardial infarction[15]. Glycosylated haemoglobin is considered to be a fairly accurate indicator of long-term glycaemic control as it reflects the history of control over the previous two to three months. The high diabetes prevalence accompanied by poor glycemic control and deranged lipid parameters places the Asian Indian community at extremely high cardiovascular risk and explains the epidemic of CAD and premature atherosclerosis in this ethnic group. Unless serious population health measures are instituted urgently, this bodes very poorly for this ethnic group. It is never too late to implement interventional measures to promote an active lifestyle, reducing obesity and increasing physical activity, in an attempt to prevent diabetes, since improved glycaemic control, translating into reduced HBA1c, has been shown to be associated with reduced risk or a delay in the development of cardiovascular complications[27]. Aggressive lifestyle modification must be advocated in this very high-risk community, and should begin at school-going age [14].

Funding information:

This research was funded by a grant from WHO (Africa Division), Servier and Pfizer laboratories.

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