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Insulin resistance and acute glucose changes determine arterial elastic properties and coronary flow reserve in dysglycaemic and first-degree relatives of diabetic patients

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ABSTRACT

Background: Insulin resistance is linked to endothelial dysfunction. We investigated whether first-degree relatives of type-2 diabetes patients (FDR) present differences in vascular function at baseline and during postprandial hyperglycemia compared to dysglycaemic or normoglycaemic subjects.
Methods: We studied 40 FDR with normal oral glucose test (OGTT), 40 subjects with abnormal OGTT (dysglycaemic) and 20 subjects with normal OGTT without parental history of diabetes (normoglycaemic) with similar clinical characteristics. Glucose, insulin, pulse wave velocity (PWV), central systolic blood pressure (cSBP) and augmentation index (AI) were measured at 0, 30, 60, 90 and 120min during OGTT. Coronary flow reserve (CFR) was assessed using Doppler echocardiography at 0 and 120min after OGTT. Insulin sensitivity was evaluated using Matsuda and insulin sensitivity index (ISI).
Results: FDR and dysglycaemics had higher fasting insulin, reduced ISI, Matsuda index as well as reduced CFR (2.54 ± 0.5 vs. 2.45 ± 0.3 vs. 2.74 ± 0.5), increased PWV, (8.9 ± 1.1 vs. 10.3 ± 2.4vs. 8.0 ± 1.5 m/sec), AI (23.8 ± 13.6 vs. 26.5 ± 14.4vs.17.7 $\pm$ 14%) and cSBP than normoglycaemics ($p < 0.05$ for all comparisons). During OGTT, AI was similarly reduced in both normoglycaemic and FDR ($p < 0.05$) at peak insulin levels (60 min) though FDR had 2-fold higher insulin than normoglycaemics. AI was increased in dysglycaemics after peak glucose levels, at 120 min ($p < 0.05$). CFR was reduced by 10% and 15% at 120min in FDR and dysglycaemic respectively, while remained unchanged in normoglycaemics ($p < 0.05$). The percent reduction of CFR was related with the percent increase of glucose levels, ISI and Matsuda index($p < 0.05$).
Conclusion: First-degree relatives and dysglycaemic patients have impaired arterial and coronary microcirculatory function. Insulin resistance determines acute vascular responses during postprandial hyperglycemia.
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1. Introduction

Subclinical states of insulin resistance namely impaired glucose tolerance as well as being a first-degree relative (FDR) of a type 2 diabetic patient are considered predisposing factors for vascular disease [1,2].

Increased arterial stiffness is an independent predictor of cardiac function [3,4] atherosclerosis [5,6] and future cardiovascular events [6,7]. Increased pulse wave velocity (PWV) and augmentation index (AI) are markers of arterial stiffness and wave reflections respectively and have been found to be related with insulin resistance [8]. Previous studies have shown that the acute improvement of arterial stiffness and wave reflections after acute insulin elevation is abolished in diabetes mellitus and in states of insulin resistance [9,10]. Insulin resistance has been demonstrated in healthy first degree relatives of diabetic patients [11].

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Coronary flow reserve (CFR) is a marker the coronary microcirculatory function even in the presence of epicardial coronary artery stenosis [12,13] and has also an independent prognostic value for future cardiovascular events [14]. CFR has been found impaired in type 2 diabetic patients [15,16].

However, the association of arterial wall properties and CFR with insulin resistance and postprandial hyperglycemia in first degree relatives of diabetic subjects has not been clearly defined.

We hypothesized that first degree relatives (FDR) of type 2 diabetic patients have impaired arterial wall elastic properties and coronary flow reserve compared to subjects with normal oral glucose tolerance test (OGTT) (normoglycaemic) and similar vascular responses to acute hyperglycemia-insulinemia with subjects with abnormal OGTT (dysglycaemic) because of the development of insulin resistance.

The aim of the present study was to investigate a) the differences in baseline arterial stiffness, central aortic pressures, wave reflections, coronary flow reserve and indices of insulin resistance between first degree relatives of diabetic patients, normoglycaemic and dysglycaemic subjects b) the acute changes of vascular markers in relation to the corresponding changes of glucose and insulin after postprandial hyperglycemia provoked during a 2 h oral glucose tolerance test.

2. Methods

2.1. Study population

The study population consisted of 40 first degree relatives of type 2 diabetic patients (at least one parent with diabetes) with normal results of a 75gr-OGTT matched for age-and sex with 40 subjects with abnormal OGTT (dysglycaemic subjects) (Table 1). Twenty normoglycaemic patients with similar age and sex, normal OGTT and no parental history of diabetes served as controls. Propensity score analysis was used to secure that the 3 study groups were adequately balanced for traditional atherosclerotic risk factors waist and hips circumference and BMI. Normoglycaemic status was defined as a fasting glucose levels <110 mg/dL in the absence of use antidiabetic medications and glucose levels <140 mg/dl at the 2-h sample of the OGTT [18]. The fasting and OGTT glucose levels were within the normal range in FDR and normoglycaemic subjects in the present study. All dysglycaemic subjects had glucose levels >140 mg/dl at the 2-h sample of the OGTT. Exclusion criteria were history or clinical evidence of coronary or valvular heart disease, congestive heart failure, peripheral vascular disease, liver or kidney failure, history of alcohol or drug abuse, and treatments able to modify glucose metabolism. All women were premenopausal and their investigations were undertaken during the first week of their menstrual cycles. None of them were taking oral contraceptives. Dyslipidemia was defined as cholesterol>220 mg/dl and or triglycerides >150 mg/dl. Hypertension was defined as clinic BP > 140/90 mmHg. Height, weight, body mass index (BMI) waist, and hips circumference were determined for all participants.) The study was approved by the hospital's research committee, and all subjects provided writer informed consent.

2.2. Laboratory measurements

Plasma glucose was measured by the enzymatic in vitro test (Roche, automatic chemistry clinical analyzer). Serum insulin concentration was determined by a chemiluminescense-based assay (Roche Diagnostics).

In all subjects a standard 75-gr OGTT was performed. Venous blood was sampled at 0, 30, 60, 90, and 120 min after glucose load to determine plasma glucose and serum insulin. Glucose tolerance status was defined on the basis of OGTT using the Word Health Organization (WHO) criteria. Normal glucose tolerance is when 2-h sample results of the OGTT are <140 mg/dl and impaired glucose tolerance is when 2-h sample results of the OGTT are between 140 and 199 mg/dl. A 2-h postload glucose levels ≥200 mg/dl is diagnostic of diabetes mellitus. The OGTT results were within the normal range [17] in FDR and normoglycaemic subjects in the present study. We measured insulin resistance during OGTT using the Matsuda index and the insulin sensitivity index (ISI). The Matsuda index calculated as follows: 10,000/square root of [fasting glucose (mmol/L) × fasting insulin (mU/L)] × [mean glucose × mean insulin during OGTT]. The Matsuda index is strongly related to euglycemic hyperinsulinemic clamp that represents the gold standard test for measuring insulin sensitivity [18]. The ISI is a quantitative method for measuring the resistance of insulin and calculated by the formula: $ISI_{0,120} = 75{,}000 + (G_0 - G_{120}) \times 0.19 \times m/120 \times G_{mean} \times Log\ (I_{mean})$ [G_0 = Glucose at 0 min and

Table 1
Demographic and biochemical profile of the study population.

	Normoglycaemic subjects	First degree relatives	Dysglycaemic subjects	P
N	20	40	40	
Age, y	37 ± 8	39 ± 7	43 ± 8	0.410
Male sex, n (%)	12 (60)	22 (55)	22 (55)	0.833
Current smoker, n (%)	8 (40)	17 (43)	16 (40)	0.856
Hypertension, n (%)	3 (15)	6 (15)	6 (15)	0.999
Dyslipidemia, n (%)	8 (40)	16 (40)	17 (43)	0.856
BMI, kg/m^2	28.7 ± 4.1	29.1 ± 5.0	29.9 ± 3.9‡‡‡	0.834
Waist, cm	100.4 ± 13.3	101.2 ± 14.3	102.7 ± 12,1	0.251
Hips, cm	101.2 ± 10.8	104.7 ± 12.5	106.9 ± 9.4	0.201
Propensity scores	0.185 ± 0.093	0.190 ± 0.093	0.195 ± 0.093	0.735
Fasting glucose, mg/dL	91.1 ± 11.0	94.5 ± 7.2**	115.1 ± 26.7***	<0.001
Peak glucose, mg/dL	137.8 ± 23.6*	154.6 ± 21.7**	225.3 ± 48.4***	<0.001
2h OGTT glucose, mg/dL	98.7 ± 15.5‡	106.5 ± 16.1**	200.71 ± 50.4***	<0.001
Fasting insulin, μU/ml	8.2 ± 2.8*	16.6 ± 8.0	15.1 ± 12.4‡‡‡	0.034
Peak insulin, μU/ml	58.1 ± 30.3*	119.2 ± 72.2	106.4 ± 88.0‡‡‡	0.011
2h OGTT insulin, μU/ml	29.5 ± 13.8*	58.0 ± 33.0‡‡	79.4 ± 70.9††	0.001
ISI	94.3 ± 17.1†	75.2 ± 19.6**	39.0 ± 13.4***	<0.001
Matsuda Index	5.5 ± 1.5*	3.0 ± 1.2	2.9 ± 1.7***	<0.001

Data are presented as mean ± SD values. Normoglycaemic: normal 2 h OGTT, no history of diabetes, Dysglycaemic: abnormal OGTT, First degree relatives: normal OGTT and parental history of diabetes BMI: body mass index, OGTT: oral glucose tolerance test; ISI: insulin sensitivity index. P: p of model of the ANOVA or contingency table for comparisons between groups. *p < 0.001, †p = 0.001, ‡p < 0.05 for comparisons of normoglycaemic subjects vs first degree relatives **p < 0.001, ‡‡p < 0.05 for first degree relatives vs. dysglycaemic subjects***p < 0.001, ††p = 0.001, ‡‡‡p < 0.05, for dysglycaemic vs. normoglycaemic subjects by post-hoc analysis with Bonferoni correction. The model was adjusted for age, sex, smoking, dyslipidemia, BMI, waist circumference, hips circumference systolic or diastolic blood pressure.