Original Article

Genetic Association Between Insulin Resistance And Total Cholesterol In Type 2 Diabetes Mellitus - A Preliminary Observation

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Abstract:

We investigated the degree of genetic association between insulin resistance (IR) with type 2 diabetes mellitus (DM) and abnormalities in lipid metabolism in 42 patients. IR was assessed by fasting insulin test (FI), McAuley (McA), HOMA and QUICKI methods. IR was detected in 34 (81%) patients by FI, McA and in 39 (93%) patients by HOMA and QUICKI. 26 (62%) patients had family history of DM and 23 (89%) of them displayed IR by FI & McA. 24 of them (92%) displayed IR by HOMA and QUICKI. Our results suggest that association between the family history of DM and IR were statistically significant by chi-square test (P<0.05). Further, 29 (69%) patients had elevated total cholesterol levels. Association between elevated total cholesterol and IR as assessed by FI test was also statistically significant (x^2=4.6; p<0.05).

Results of our study indicate the statistically significant genetic association of IR with abnormal cholesterol metabolism and family history of DM.

Key Words: Type 2 diabetes, Insulin resistance, McAuley index, Dyslipidaemia

Introduction

Type 2 diabetes mellitus (DM) is a common metabolic disorder characterized by insulin resistance (IR).(1) Strong evidence favors the role of genetic factors in the development of DM, resulting in a higher risk of developing DM in individuals with a strong family history of DM.(2) Concordance rate of DM in monozygotic twins ranges from 55% to 90%.(3) In addition, normoglycaemic subjects with a strong family history of DM display IR.(3) IR is a pathological condition characterized by the lack of physiological response of peripheral tissues to insulin, leading to metabolic and hemodynamic disturbances known as the metabolic syndrome.(4) Main features of this syndrome include dyslipidemia, hypertension, increased incidence of coronary heart disease, DM, hyperuricemia, abdominal obesity, defects in the fibrinolytic system, hyperandrogenism and fatty liver.(4) The interest of the IR and the metabolic syndrome lies in their high prevalence in the population and the associated high death rate, fundamentally through coronary heart disease, even in non-diabetic subjects.(5,6) The association between IR, hyperinsulinemia and coronary heart disease is well established.(5,6)

Early detection and intervention of IR can prevent or delay the decline in ß cell function and thereby lowering the burden of DM. However, difficulties in measuring insulin sensitivity prevent the identification of insulin resistant individuals in the general population. Quantification of IR can be performed by evaluating the peripheral insulin sensitivity *in vivo* by hyperinsulinemic euglycemic clamp technique and pancreatic suppression test.(7) They are complicated, time consuming and expensive methods suitable only for studies with a small number of subjects. For epidemiological and clinical studies, more simple methods such as McAuley index (McA), HOMA index (HOMA), QUICKI index (QUICKI) have been advocated for the quantification of IR, based on the mathematical calculations using fasting insulin (FI), fasting blood glucose (FBS) and triglyceride levels.(8)

Data related to the prevalence and quantitative analysis of IR and prevalence of dyslipidemia among Sri Lankan diabetic population are not available. Therefore, we planned to identify the genetic association of IR with DM and the dyslipidemia by using the above simple methods in Sri Lankan diabetic population.

Materials and Methods

Forty two diabetic patients who attended a medical clinic in private sector during the year 2004 were recruited to our study after obtaining their informed written consent. Diagnostic criteria for DM were fasting blood glucose of (FBS) >7mmol/L (126 mg/dL) on one occasion in symptomatic patients or two occasions in asymptomatic patients. Clinical history was obtained from all subjects including age, sex, personal medical history and intake of drugs. Following exclusion criteria were used in this study: age out side the range of 20-65 years, liver, kidney or heart failure and neoplasia. Blood samples were collected from the patients after a 12-hour overnight fast. Plasma was separated immediately by refrigerated centrifugation at 4000 rpm for a period of 10 minutes. The samples were analyzed either immediately or during the first week after conservation at -20^0C. Fasting blood glucose (Diagnostica–Merck), insulin (ELISA–Diagnostic–Automation), triglycerides (TG) and total cholesterol (LABKIT– P & T Diagnostics) concentrations were measured in all subjects. IR was assessed in each patient by fasting insulin test (FI), McA, HOMA and QUICKI.

McA, HOMA and QUICKI were calculated using following equations.(8-10)

McAuley = exp [2.63 – 0.28 ln (insulin in mU/L) – 0.31 ln (triglycerides in mmol/L)]

HOMA = insulin (μU/m) x [glucose (mmol/L)/22.5]

$$QUICKI = \frac{1}{\log \text{insulin} + \log \text{glycemia in mg/L}}$$

Patients were considered as insulin resistant when FI=12mU/L, McA= 5.8, HOMA=2.6 and QUICKI=0.33.(10, 11)

A positive family history of DM was defined as having a first degree or second-degree relative with DM diagnosed at an adult age and not requiring insulin during the early period of diagnosis to control the condition.(8)

The study was approved by the ethical committee of Faculty of Medicine, University of Ruhuna and it was conducted in the Molecular Science and Biomedical Unit, Department of Pharmacology, Faculty of Medicine, University of Ruhuna.

Statistics

The association between family history of DM and occurrence of IR as assessed by FI was studied with the chi–square test (x^2). The association between elevated total cholesterol (ETC >220 mg/dL) and IR was also studied using x^2. All statistical analyses were performed using Microcal Origin 4.1 and Microsoft Excel whenever applicable.

Results

The general characteristics of the 42 diabetic patients comprising of 19 men and 23 women aged between 20-65 years are shown in Table 1.

Table 1: General characteristics of the study group (n=42)

Characteristics	Value
Age (years)	46 ± 2
BMI (Kg/m²)	23 ± 1
Total cholesterol (mg/dL)	248 ± 8
Triglyceride (mg/dL)	158 ± 6
HDL cholesterol (mg/dL)	57 ± 2
LDL cholesterol (mg/dL)	158 ± 8
Fasting blood glucose (mg/dL)	179 ± 10
Fasting nsulin (mU/L)	38 ± 5
McAuly index	4 ± 0.2
HOMA index	18 ± 2.5
QUICKI index	0.3 ± 0.01

Insulin resistance was analyzed in each patient by different methods of measuring insulin resistance using the criteria given under each method. Numbers of insulin resistant and sensitive patients according to the above methods are shown in Table 2.

Table 2: Insulin resistance according to different methods of measuring insulin resistance (n=42)

Index	Number of insulin resistant patients	Number of insulin sensitive patients
Fasting insulin	34	8
McAuley index	34	8
HOMA index	39	3
QUICKI index	39	3

Our results show that 26 of 42 patients had a family history of DM. 23 of them had a positive family history of DM among their first-degree relatives. Figure 1 shows the number and the percentage of insulin

resistant patients according to the results of different methods of measuring insulin resistance in relation to the presence or absence of family history of DM. 24 of 26 positive family history patients (92%) were insulin resistant while 10 of 16 negative family history patients (62%) were insulin resistant by FI and McA methods. All the patients with positive family history (26/26) were insulin resistant and 13 of 16 negative family history patients (81%) were insulin resistant by HOMA and QUICKI methods.
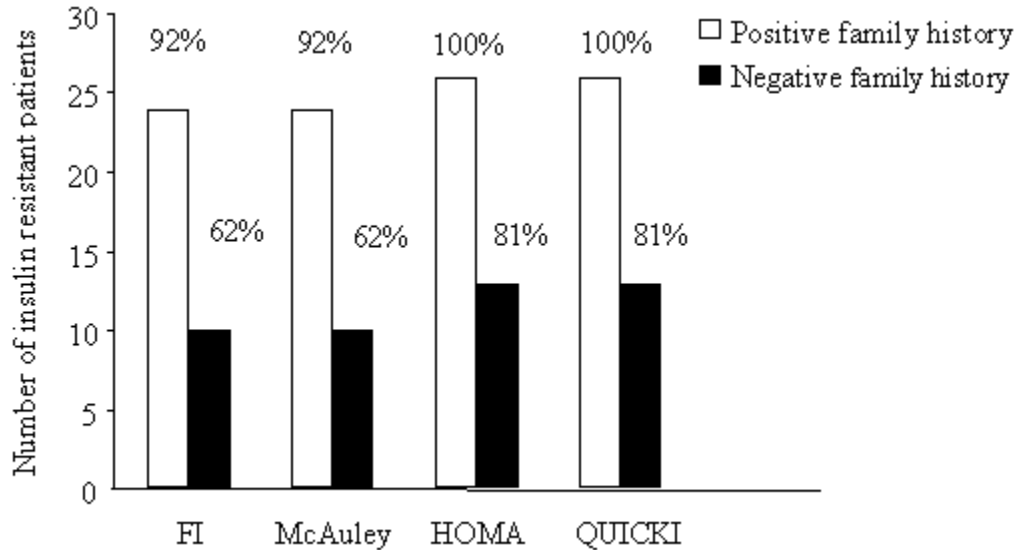

Figure 1: Number of insulin resistant patients according to the different methods of measuring insulin resistance in relation to the family history of DM

Table 3 shows the statistical association between patients with a positive family history of DM and IR. There was a statistically significant association between the family history of DM and IR values obtained by all the methods.

Table 3: Association between family history of diabetes mellitus and insulin resistance by fasting insulin, McAuley, HOMA and QUICKI indices

Variables	X^2 (chi-square value)	Probability
Family history and fasting insulin	7.65	<0.01
Family history and McAuley	5.71	<0.05
Family history and HOMA	5.25	<0.05
Family history and QUICKI	5.25	<0.05

The association between total cholesterol and IR was examined in our study group. There were 29 patients (69%) with elevated total cholesterol levels (>220 mg/dL) and 26 (89%) of them were insulin resistant by FI test. Table 4 shows the significant association between elevated total cholesterol and the IR by FI test (x^2=4.6, p<0.05). In contrast, there was no significant association between elevated total cholesterol and other IR values obtained by McA, HOMA and QUICKI indices (data not shown). Further, we could not detect any significant association between IR and triglyceride levels (data not shown) in our study group.

Table 4: Association between elevated total cholesterol and insulin resistance by fasting insulin (n=42)

Variables	X^2 (chi-square value)	Probability
Elevated total cholesterol (=220 mg/dL) and FI (=12 mU/L)	4.6	p< 0.05

Discussion

We planned to identify the genetic association of IR with DM and the dyslipidemia because the data related to the prevalence and quantitative analysis of IR and prevalence of dyslipidemia among Sri Lankan diabetic population are not available. Previous reports says early detection of IR in apparently normal individuals in the population is important for diabetes intervention programs, which are more likely to be successful at an early stage rather than later.(8) In addition, reports show that many clinical and metabolic abnormalities are significantly associated with IR.(13) Moreover, the metabolic syndrome, a condition pathophysiologically related to IR, also has an elevated prevalence in adult population, varying from 0.8 to 35.3%, after adjustment for age and the criteria used for establishing the diagnosis.(15) A recent study by American Diabetic Association has shown that IR can be detected in up to 31.8% of normal adult population.(14)

Our results show that IR was detected by FI and McA up to 81% of diabetic population whereas it was detected by HOMA and QUICKI in 93% of patients. Further, we attempted to find out the association between occurrence of IR and abnormalities of lipid profiles. Here we found that the association between elevated total cholesterol and IR as assessed by FI test is statistically significant but not with triglyceride, LDL cholesterol or HDL cholesterol. In contrast, we could not find any significant association between elevated total cholesterol and IR assessed by McA, HOMA and QUICKI methods. HOMA and QUICKI values depend on FBS in addition to the fasting insulin. FBS is a variable factor in this group of patients because they are on hypoglycaemic drugs. Treatment can vary the FBS as well as the results obtained by HOMA and QUICKI in this group. The index proposed by McAuley et al (5) for the diagnosis of IR consists of a score based on fasting triglycerides in addition to the fasting insulin levels. Absence of any significant association of elevated total cholesterol with IR assessed by McA can be explained by its inclusion of TG as a fundamental parameter in the equation.

Taken together our results show that the genetic association between DM and IR is statistically significant. There is also statistically significant association between IR by FI test and the elevated total cholesterol levels. However, there was no significant association between occurrence of IR and triglyceride, LDL cholesterol or HDL cholesterol. Therefore, the association between elevated total cholesterol and IR could be due to the effects of IR on cholesterol metabolism or vice versa. A significant finding of this study is that there is a qualitative association between IR and elevated total cholesterol, but not with the other components of lipid profile. We hereby recommend large-scale studies for the confirmation of our findings because our sample size is small and our conclusion need to be confirmed with an adequate sample.

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