The insulin resistance syndrome among type II diabetics

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ABSTRACT

Objective: The aim of this study is to determine the prevalence of insulin resistance syndrome among type-II Saudi diabetics.

Methods. The study involved type-II Saudi diabetics followed at the Out-patient Clinic of King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia, from January 1997 to December 1998. Their age, sex and body mass index was recorded. Serum samples were analyzed for glucose. Insulin C-peptide level and insulin glucose index was calculated. Serum cholesterol, high density lipoproteins, low density lipoproteins, triglyceride, and uric acid were measured.

Results. A total of 109 patients were studied, (67 females and 42 males) with an age range from 28 to 105 years. Median body mass index was 27 in males and 30.2 in females. Percentage of male and female patients with the following abnormalities were as follows: Total cholesterol >5.3mmol/L (47.6% males, 40.9% females), high density lipoproteins-cholesterol <1.2mmol/L (71.4% males, 40.9% females), low density lipoproteins-cholesterol >3.4mmol/L (42.8% males, 37.9% females), triglyceride >2.3mmol/L (40.5% males, 31.8% females), insulin >24mIU/l (23.8% males, 29.7% females), C-peptide >1324 pmol/L (21.2% males, 13% females) and hypertension (33.3% males, 43.8% females). Uric acid >420umol/L was found in 35.5% males and >390umol/L in 25.6% females. Body mass index >27.8 was found in males (35.7%) and >27.3 in females (67.7%). Insulin resistance as defined by insulin glucose index >5.4 was found in 19.8% of the study group (23.8% males, 15.9% females). Insulin resistance syndrome was found in 16.5% (17.1% males, 15.9% females).

Conclusion: Insulin resistance syndrome is common among type-II Saudi diabetics.

Keywords: Insulin resistance syndrome, non-insulin dependent diabetes mellitus, diabetic.

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Insulin resistance has long been recognized and was initially defined as the requirement of very high doses of insulin (>200 units/day)[1] to maintain euglycemia. Now the term insulin resistance is used to describe any reduction in the biological response to insulin. The first direct reference to the concept of sensitivity or resistance to insulin was made by Himsworth in the mid 30s.[2] Hollenbeck and Reaven[3] found that insulin sensitivity can vary among individuals with normal glucose tolerance and that almost 25% of individual in good health, who were not overweight and who had normal glucose tolerance, presented a degree of insulin resistance which was comparable to that observed in patients with type II diabetes mellitus (DM). Interest in insulin resistance increased further with the recognition that it is also associated with hyperlipidemia, hypertension and cardiovascular

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disease in non-diabetics as well as in non-insulin dependent diabetes mellitus (NIDDM). Reaven[4] in his famous Banting lecture in 1988 was the first to coin the term Syndrome X, which is a syndrome of insulin resistance in NIDDM associated with hyperlipidemia, hypertension, obesity (especially central or truncal), and cardiovascular disease. The insulin resistance syndrome or syndrome x has been studied in many different populations[5-8] with some differences in manifestation according to risks of diabetes and cardiovascular disease. Type II diabetes are usually characterized by peripheral insulin-resistance, B-cell failure, and increased hepatic glucose production[9] and hence many studies have shown insulin-resistance with type II diabetics.[10,11] Some have also reported an association of insulin-resistance with higher blood pressure and dyslipidemia (increased triglyceride and decreased high density lipoprotein (HDL) cholesterol).[12] Non-insulin dependent DM or type II diabetes is a major health problem in Kingdom of Saudi Arabia (KSA) with increasing prevalence over the past decade or so, from 5-11.8%.[13,14] Although, the environmental factors of increased caloric intake reduced physical activity and obesity play a major role in this increase, consanguinity is still common and thus a strong genetic determination is also of importance. Practicing physicians working in KSA noted not only the increasing prevalence of NIDDM, but also of hypertension, cardiovascular diseases, obesity and hyperlipidemia (Personal communications). The aim of this study is to determine the prevalence insulin resistance syndrome among Saudi patients with NIDDM.

Methods. The study investigated 109 Saudi patients (67 females and 42 males) with type II DM. These patients were recruited following consent and with Ethical Committee approval, from our out-patient medical clinics. Patients' weight, height and blood pressure were all recorded during the initial visit.

Biochemical analysis. Fasting blood samples were collected into plain tube (5ml), and tubes containing ethylene diamine tetraacytic acid (EDTA) anticoagulant (5ml). Serum samples were immediately analyzed for glucose, uric acid, cholesterol, HDL-cholesterol, and triglycerides, whereas samples for glycohemoglobin (HBA1c) measurements were batched and assayed using the EDTA tubes. Analysis of all tests was performed on the 911 Hitachi autoanalyzer (Hoffmann-La Roche - BM, Germany). Using Hexokinase method for glucose, uricase for uric acid, cholesterol oxidase for cholesterol, and immunoassay for HBA1c. Analysis was according to the manufacturer's instructions. Low density lipoprotein (LDL)-cholesterol values were calculated using the Friedwald et al formula[15] for samples with triglyceride levels not exceeding 4.5 mmol/L. Data analysis was performed using in-house statistics computer software. Shapiro test[16] by Royston was used to test data obtained for normality. Wilcoxon rank test was used for non-parametric distribution and median and range values reported. Serum aliquots for insulin and C-peptide measurements were stored at -70°C until analyzed by solid phase radio immunoassay and double antibody competitive radio immunoassay respectively (DPC, Los Angeles, CA, United States of America). Samples were assayed in duplicates and mean values was recorded. The assay procedures were performed according to the supplier's instructions. Imprecision for both assays was less than 11.2%. Insulin glucose index was calculated for each patient in the study. This was determined by estimating the relative insulin glucose ratio (index) as described.[17]

Results. One hundred and nine patients were entered into the study. Patients' characteristics are shown in **Table 1**. Although males had significantly ($P<0.005$) higher age and height than females, the difference in weight was, however, not significant ($P=0.14$). Significantly, higher body mass index (BMI) was observed in females compared to males ($P<0.01$). Hypertension was observed in 43.8% of females compared with 33.3% in males. Results for the biochemical parameters measured are shown in **Table 2**. Patients' characteristics and biochemical parameters were tested for normality. Data not exhibiting Gaussian distribution were analyzed using Wilcoxon non-parametric test. There were no significant sex differences in fasting insulin, C-peptide, insulin glucose ratio, total cholesterol, LDL-cholesterol, and triglyceride. Fasting blood glucose and HDL-cholesterol were significantly higher in

Table 1 - Median and range values for patients' characteristics. Statistical significance (P values) for differences between males and females.

Patients characteristics	Median	Significance
Age range (years)		
Male (33-105)	56	
Female (28-80)	50	P<0.005
Weight range (kg)		
Male (46-117)	74.8	
Female (45-111)	71	P=0.14
Height range (m)		
Male (1.52 - 1.85)	1.65	
Female (1.37 - 1.67)	1.54	P<0.005
Body mass index range		
Male (17.9 - 50.2)	27	
Female (20.2 - 42.3)	30.2	P<0.01

Table 2 - Median and range values for all biochemical parameters. Statistical significance (P-value) between males and females for each parameter.

Patients' characteristics	Male		Female		Significance
	Median	Range	Median	Range	
Insulin (mIU/L)	15.7	(1.1 - 247.7)	11.2	(1.4 - 334.1)	P=0.347
C-peptide (pmol/L)	397.2	(4.5 - 2813.5)	364.8	(6.0 - 4303)	P=0.55
Glucose (mmol/L)	8.4	(1.9 - 22.7)	9.4	(4.2 - 24.0)	P<0.095
Insulin/glucose ratio	1.78	(0.10 - 30.96)	1.37	(0.06 - 21.28)	P=0.190
Uric acid (umol/L)	372	(115.00 - 819)	262	(109.00 - 790)	P<0.003
Total cholesterol (mmol/L)	5.05	(2.38 - 9.26)	4.99	(2.44 - 9.90)	P=0.6
HDL-cholesterol (mmol/L)	0.93	(0.26 - 4.26)	1.09	(0.32 - 2.08)	P<0.005
LDL-cholesterol* (mmol/L)	3.36	(1.03 - 6.5)	3.20	(1.0 - 8.62)	P=0.98
Triglycerides (mmol/L)	1.88	(0.63 - 9.59)	1.83	(0.71 - 6.30)	P=0.24

HDL - high density lipoproteins, LDL - low density lipoproteins, * calculated

females compared to males, whereas serum uric acid levels were significantly lower in female subjects (**Table 2**). Percentage of male and female patients with the following abnormalities were as follows; total cholesterol >5.2 mmol/L (47.6% males, 40.9% females), HDL-cholesterol <1.2 mmol/L (71.4% males, 40.9% females), LDL-cholesterol >3.4 mmol/L (42.8% males, 37.9% females), triglycerides >2.3 mmol/L (40.5% males, 31.8% females), insulin >24mIU/L (23.8% males, 29.7% females), C-peptide >1324 pmol/L (21.2% males, 13.0% females), among study patients. The percentage of males patients with uric acid >420 umol/L was 35.5% compared with uric acid >390 umol/L among females of 25.6%. Body mass index (BMI) >27.8 kg/m^2 in males and >27.3 kg/m^2 in females was found in 35.7% and 67.7% of each group respectively. Hypertension was observed in 33.3% of males compared with 43.8% in females. Percentage of male patients with insulin resistance as defined by insulin glucose index >5.4 (23.8% males, 15.9% females). Based on the Reaven's criteria,[3] the percentage of patients in this study classified, as having insulin resistance syndrome was 16.5% (17.1% male subjects and 15.9% female subjects).

Discussion. This study investigated the prevalence of insulin resistance among Saudi patients with type II DM. Although the prevalence of type II DM itself has doubled in KSA over the past decade from 4.95%[13] to 11.8%,[14] the incidence of insulin resistance and its contribution to DM is not known. The National Chronic Metabolic Disease Survey (NCMDS) conducted by the Ministry of Health in KSA[14] also found a high prevalence of obesity (16% male, 24% female), compared with data obtained in this study (14.3% males, 26.2% females). There were more women than men in this study and although there was no significant sex differences in weight, the age, height and basal metabolic index were different. Furthermore, there were no significant sex differences in the biochemical parameters measured in our patients except for fasting glucose, uric acid and HDL-Cholesterol. Furthermore in our study, patients' hypertension was more common in females compared to males. The overall prevalence of the insulin resistance syndrome in the studied group was 16.5% (male patients has 17.1% and female has 15.9%). The NCMDS showed the presence of DM, obesity and hypercholesterolemia of >5.2 mmol/L (in 9-11%), all of these findings suggest that the insulin resistance syndrome might be significantly found amongst our diabetic population. This could be referred from our result which showed an increased BMI >27.8 kg/m^2 in men and >27.3 kg/m^3 in women in 54.6% of our patients. Hypercholesterolemia >5.2 mmol/L was also found in 43.5% of our patients and hypertriglyceridemia of >3.4 in 35.2% of our patients. The study provides data which supports the presence of insulin resistance syndrome in type II Saudi diabetic. Of the 109 patients, approximately 16.5% were found with insulin resistance syndrome. This is evidenced by the high insulin glucose index (>5.4) and hyperinsulinemia. Although insulin actions are many, studies on insulin resistance have focused mainly on its effect on circulating glucose

levels. Shen et al and Reaven[18-20] described insulin resistance as a relative impairment of insulin-mediated uptake of glucose by tissues (predominantly muscle). Whereas Khan[21] proposed a wider definition of resistance being that of normal concentrations of the hormones produce a less than normal biological response, this wider definition encompasses other biological effects on insulin. Assessment of dose response curve is essential and requirement to study effects across a range of insulin concentrations is difficult and can not be easily applied to population studies. Several methods had been developed to measure insulin resistance in vivo, they include static test (fasting plasma insulin concentrations and homeostasis model assessment where insulin – glucose product is obtained from the measurement of 3 samples taken over 10 minutes. These tests are simple to perform and are widely used in large studies compared with dynamic tests such as glucose tolerance tests and hyperglycemic clamp, euglycemic hyperinsulinemic clamp and short insulin tolerance test among others. In some studies hyperinsulinemia alone was considered as a marker of insulin resistance, however, not all patients with documented insulin resistance had hyperinsulinism, thus hyperinsulinism on it own can only be regarded as a surrogate of insulin resistance. The insulin immunoassay used in this study was reported to show no cross reactivity with pro-insulin and intermediate precursors[22] a source of error and discrepancy in a number of earlier studies. It is clear that the insulin resistance syndrome is prevalent in Saudi Type II Diabetics, but that more patients are needed to be studied to further clarify this.

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