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Full Length Research Paper

Determination of insulin resistance in non-diabetic Saudi adults by including fasting free fatty acids into QUICKI

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Most available diagnostic methods of insulin resistance are either unsuitable for screening or fail to detect marginal cases. It was reported that including plasma free fatty acids (FFA) into QUICK (quantitative insulin sensitivity check index) I improves its diagnostic power. The aim was to test the effectiveness of modified QUICK I against HOMA (homeostasis model assessment) and QUICK I in identifying insulin resistant subjects in the non-diabetic adult population. 357 healthy adults aged 18 - 50 years were recruited randomly. Their anthropometric and demographic information were taken. Biochemical parameters and FFA (free fatty acid) were measured in fasting blood samples and used to calculate modified QUICK I. Reported cut-off point was used to identify IR subjects, who were matched for age and sex to individuals from the rest of the subjects. 209 subjects satisfied the criteria. 97 individuals were identified to be IR. This group had statistically different anthropometric and biochemical parameters compared to NIR group. Biochemical parameters did not differ significantly when QUICK I was used to identify IR subjects. The modified QUICK I for all subjects correlated significantly (p = 0.01) with HOMA values (r = -0.756) and with QUICK I values (r = 0.758). Modified QUICK I is a more powerful diagnostic index of IR in Saudi non diabetic adults.

Key words: Insulin resistance, non diabetic, QUICK, FFA.

INTRODUCTION

Insulin resistance underlies abnormalities of glucose, lipid and blood pressure homeostasis (Caro, 1991). It is also the major factor involved in the pathogenesis of several diseases including type 2 diabetes, hypertension, dyslipidemias and cardiovascular disorders (Reaven, 1998). There is an increasing prevalence of these diseases in the kingdom of Saudi Arabia (Al Nuaim et al., 1995; Mira et al., 2002). A recent survey (Al-Nozha et al., 2004) stated that the prevalence of diabetes mellitus in the Kingdom has reached 23.7% in adults. Various studies showed that insulin resistance is the stronger predictive factor of the future development of the disease (Lillioja et al., 1993; Martin et al., 1992). In a recent study (Mira et al., 2002), the prevalence of resistance was estimated in type 2 Saudi diabetics and was found to be 19.8% in the studied population.

Therefore, identification of insulin resistant subjects in the general non diabetic population is of great importance in the community based strategy to reduce its prevalence and hence the prevalence of NIDDM. The method of choice has to be suitable for large population study requiring one blood sample only and has high level of reproducibility and prediction power as well as being easily interpreted.

In humans, the "gold standard" for assessing insulin resistance is the euglycemic hyperinsulinemic clamp (IS clamp) because it directly measures the insulin action on glucose utilization under steady-state conditions. However, this technique is difficult and can only be used for small number of subjects (Defronzo et al., 1979).

There are number of other more practical methods used in research and clinical larger scale settings. The most popular measures are the HOMA and the QUICKI.

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Both correlate reasonably with the clamp technique (Katz et al., 2000; Abbasi and Reaven, 2002), but both have limitations also (Abbasi and Reaven, 2002; Hanson et al., 2000; Mather et al., 2001).

More recently, Perseghin et al. (2001) by incorporating fasting plasma free fatty acid (FFA) concentration into QUICK I (modified QUICKI = 1/[log(fasting insulin) + log(fasting blood glucose) + log (fasting FFA)], improved its correlation to the IS clamp and its discriminatory power in cases of mild insulin resistant states (Rabasa-Lhoret et al., 2003).

The aim of this study is to test the effectiveness of modified QUICKI, compared to HOMA and QUICKI, in identifying insulin resistant subjects in the non-diabetic adult population, working under the assumption that if diagnosis is correct, well recognized characteristics of insulin resistance would be significantly different in selected insulin resistant group (IR) compared to non insulin resistant group (NIR).

METHODS

A cross-sectional study design was implemented. Healthy subjects aged 18 - 50 years were recruited randomly from individuals visiting health centers July 2005 - January 2007. 6 health centers (representing the 6 health sectors of Jeddah) were chosen using a computer program and according to population density a sample size was calculated to give a total number of 357 subjects. Exclusion criteria include diabetes, endocrine disorders, hypertension, reported hyperlipidaemia and coronary heart diseases. Informed consents were obtained from the study participants. Recruits were checked for hypertension and only normotensive individuals were interviewed for demographic information. Their anthropometric measurements were taken also. They were given an appointment for blood collection. After sample collection biochemical measurements (fasting glucose, insulin, FFA) and lipids profile) were performed and the modified QUICKI calculated. Individuals whose samples had a value < the mean -2SD reported by Perseghin et al. (2001) for non diabetic subjects were labeled IR. They were matched for age and sex to individuals from the rest of the study population. An ethical approval was approved by the bioethical and research committee of KAUH.

Hypertension was defined as a systolic blood pressure above 140 mm Hg, or diastolic blood pressure above 90 mmHg respectively, or current use of antihypertensive medication. Dyslipidaemia was defined as total cholesterol level ≥ 5.2 mmol/l, a LDL-C ≥ 3.36 mmol/l and/or a HDL-C < 1.04 mmol/l. Abdominal obesity was defined as > 80 cm in females and > 94 cm in males.

Glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides (TG) were estimated using automated enzymatic methods (Dade Behring Inc, UK). Insulin was estimated using the 'electro chemiluminescence immunoassay' 'ECLIA' on modular analytics E 170 (Elecys module) immunoassay analyzer, all supplied by Roche Diagnostics GMbH. FFA was estimated manually in serum using an enzymatic method (Wako chemicals GMbH).

Descriptive statistics such as mean ± S.D. for normally distributed data or median and IQR for non-normally distributed variables were calculated for all parameters. Statistical analysis was performed using unpaired t-test and Mann Whitney-U test for comparison of normally distributed and non-normally distributed parameters respectively, while χ^2 test was used to compare categoric parameters. A statistical computer programme (SPSS) was used to analyze the data. Significance was assigned at $p < 0.05$.

RESULTS

357 subjects were recruited. Only 209 subjects satisfied the criteria and provided required samples. The demographic characteristics of the selected group are presented in Table 1. The biochemical parameters of the selected group are presented in Table 2. Using the modified QUICKI, 97 individuals were identified to be IR (that is, 46.4% of total), including 34 males (35.1%) and 63 females (64.9%).

This division between sexes was not significantly different to that in the group as a whole ($p = 0.76$). Thus, it can be concluded that sex is not a risk factor for insulin resistance. Matching for age and sex could be done for 90 subjects only. Demographic characteristics of both groups are presented in Table 3. Biochemical parameters of both groups are presented in Table 4.

To compare modified QUICKI with other more known indices, both the HOMA index and the QUICK index were calculated and used to identify likely IR individuals in the recruited population. Modified QUICKI for all subjects correlated significantly ($p = 0.01$) with HOMA values ($r = -0.756$) and with QUICKI values ($r = 0.758$). Using the HOMA index and a cut off point of > 3.8, only 26 subjects were identified, 23 of them were also identified by modified QUICKI.

The individuals identified by the HOMA index had the well recognized characteristics of IR as diagnosed by the IS clamp technique such as obesity, abdominal obesity. 22 of them (84.6%) had high total and LDL- cholesterol, fasting glucose > 6.0 - < 7.0 mmol/l, insulin, TG and FFA values in the upper quartile of the studied population.

When means or medians of demographic and biochemical characteristics of the 2 groups divided according to this index were compared statistically, significant differences were found in all cases.

Using the QUICKI and a cut off point of < 0.357, 135 subjects were identified, 84 of them were also identified by modified QUICKI. The individuals identified by the QUICKI were mostly either obese or overweight (113 individuals, or 87.7% of total) and suffered from abdominal obesity (73 individuals, or 54.1% of total). However, they did not have most of the well recognized biochemical characteristics of insulin resistance. Their calculated parameters did not significantly differ to those of the NIR group determined by modified QUICKI. Most of them had normal lipids profile, with total cholesterol ≥ 5.2 mmol/l in 47 individuals (34.8%) only, LDL-cholesterol ≥ 3.36 mmol/l in 43 subjects (31.9%) and HDL-cholesterol ≤ 1.09 mmol/l in 20 subjects (14.8%) and only 42 subjects (31.1%) having higher than acceptable plasma TG. Further more, glucose value was < 6.0 mmol/l in the majority of subjects (87 individuals, or 64.4%), and/or insulin and FFA values in the lowest quartile of the studied population.

Table 1. Demographic characteristics of the study group.

Parameter	Male	Female	Total
No. of subjects (%)	76 (36.4%)	133 (63.6%)	209(100%)
Age (yrs)	33.0 ±10.8	31.3 ± 10.2	31.8 ± 10.4
Weight (kg)	73.2 ± 16.0	67.2 ± 15.8	69.3±16.1
Height (cm)	168.0 ± 9.5	157.5 ± 7.6	161.3 ± 9.7
BMI (Kg/m^2)	25.7 ± 5.3	26.90 ± 6.5	26.44 ± 6.12
BMI classes N (%)			
Normal (<25 Kg/m^2)	37 (48.7 %)	59 (44.4 %)	96 (46.0 %)
Overweight (25 - < 30 kg/m^2)	24 (31.6 %)	35 (29.3 %)	59 (28.2 %)
Obese (≥ 30 kg/m^2)	15 (19.7 %)	39 (29.3 %)	54 (25.8 %)
Waist (cm)	87.2 ± 15.3	82.3 ± 16.4	84.6 ± 17.0
Hip (cm)	98.4 ± 15.9	105.1 ± 14.9	103.3 ± 16.1
Waist: Hip ratio	0.89± 0.015	0.78 ± 0.08	0.82 ± 0.15

BMI: body mass index.
Data are presented as mean ± SD, or number and percentage.

Table 2. Biochemical parameters of the study group.

Parameter	Male	Female	Total
No. of subjects (%)	76 (36.4%)	133 (63.6%)	209 (100%)
Total cholesterol (mmol/l)	5.1 ± 1.0	5.2 ±1.1	5.2 ± 1.1
TC ≥5.2mmol/L, N(%)	30 (39.5 %)	63 (47.4 %)	93 (44.5%)
LDL- cholesterol (mmol/l)	3.28 ± 0.76	3.02 ± 0.81	3.11 ± 0.79
LDL-cholesterol ≥ 3.36mmol/l, N (%)	32 (42. 1%)	49 (36.8 %)	81 (38.8 %)
HDL-cholesterol (mmol/l)	1.25 ± 0.29	1.58 ± 0.39	1.46 ± 0.39
HDL-cholesterol<1.09 mmol/l, N (%)	20 (26.3%)	13 (9.8%)	33 (15.8%)
TG (mmol/l)	1.32 (1.00 - 1.86)	0.99 (0.76 - 1.45)	1.1(0.8 - 1.6)
Glucose (mmol/l)	5.6 ± 0.80	5.5 ± 0.80	5.5 ± 0.80
Insulin (mU/l)	7.5 (4.4 - 14.3)	7.8 (5.7 - 11.1)	7.7 (5.3 - 11.5)
FFA (mg/dl)	8.0(5.3 - 10.8)	8.8 (6.1- 11.6)	8.4 (5.8 - 11.3)

FFA; Free fatty acids, TC; Total cholesterol, TG; Triglycerides.
Data are presented as mean ± SD for normally distributed parameters and as median and (IQR) for non-normal distributed ones.

Table 3. Demographic characteristics of insulin resistant (IR) and non insulin resistant (NIR) groups.

Parameter	IR (n = 90)	NIR (n = 90)	P
Weight (kg)	74.1± 17.9	66.5 ± 14.0	0.002
BMI (kg/m^2)	29.0 ± 7.1	25.6 ± 4.6	0
Normal (<25 kg/m^2)	26 (28.89 %)	41 (45.6 %)	
Overweight (25 - 29.9 kg/m^2)	25 (27.78 %)	34 (37.8 %)	4.29×10^{-3}
Obese (≥30 kg/m^2)	38 (42.22 %)	15 (16.7 %)	
Waist (cm)	88.5 ± 16.7	82.2 ± 14.8	0.008
Hip (cm)	105.7 ± 15.9	99.3 ± 14.5	0.006
Waist: Hip ratio	0.84 ± 0.10	0.83 ± 0.11	0.68
Waist> 88cm (F) or >102cm(M) (No.,%)	37 (41.1%)	19 (21.1%)	4.3×10^{-3}

BMI, body mass index; n, number of subjects. Continuous variables were compared by t-test and Mann Whitney-U test for comparison of normally distributed and non-normally distributed parameters. Categorical data were compared by χ^2 test.

Table 4. Biochemical parameters of insulin resistant (IR) and non insulin resistant (NIR) groups.

Parameter	IR (n = 90)	NIR (n = 90)	P
TC (mmol/l)	5.5 ± 1.1	5.0±1.0	0.003
TC ≥ 5.2mmol/l, N(%)	51 (56.6%)	31 (34.4%)	9.14×10^{-6}
LDL- cholesterol (mmol/l)	3.3 ± 0.8	2.97 ± 0.78	0.008
LDL-cholesterol ≥ 3.36mmol/l, N(%)	45 (50%)	29 (32.2%)	3.1×10^{-4}
HDL-cholesterol (mmol/l)	1.5 ± 0.4	1.5 ± 0.4	1
HDL-cholesterol<1.09 mmol/l, N(%)	13 (14.4%)	14 (14.6%)	0.77
TG (mmol/L)	1.3 (0.9 - 1.9)	1 (0.8 - 1.4)	0.002
Glucose (mmol/l)	5.7±0.8	5.4 ± 0.7	0.025
Insulin (mU/l)	11.2 (8.3 - 14.2)	6.1 (4.2 - 8.4)	0
FFA (mg/dl)	10.7 (8.4 - 13.1)	6.5 (4.8 - 9.3)	0

FFA, Free fatty acids; n, number of subjects; TC, Total cholesterol; TG, Triglycerides. Continuous variables were compared by t-test and Mann Whitney-U test for comparison of normally distributed and non normally distributed parameters. Categorical data were compared by χ^2 test.

Only 22 subjects were identified by all 3 indices. These were all obese, with abdominal obesity, abnormalities in lipid profile, blood glucose > 6.0 mmol/l, insulin and FFA levels in the upper quartile of the studied population.

DISCUSSION

Approximately 42% of the randomly recruited population had blood glucose value ≥ 7 mmol/l and had to be excluded according to our criteria. Therefore, the prevalence of diabetes in our region of the country could be much more than reported. Screening for insulin resistance and management of the condition, would help prevent, or at least delay the onset of diabetes.

Our calculated percentages of overweight and obesity in both sexes were lower than those reported by Alsaif et al. (2002).

Approximately 45% of the studied population had unacceptably high total cholesterol value (≥ 5.2 mmol/l) (Table 2). This is more than the percentage reported by Al-Nuaim (1997). Moreover, a slightly higher percentage of females were considered to be hypercholesterolaemic compared to males, which could be explained by much higher mean HDL-cholesterol in females (p = 0.000).

The high percentage of hypercholesterolaemia places our population at high risk of cardiovascular disease, with the males having a higher risk considering their higher LDL and lower HDL levels and the fact that the median triacylglycerols value was significantly higher (p = 0.021).

Almost half of our study population of non diabetic normotensive subjects were identified to be insulin resistant using the modified QUICKI and the cut off point reported by Perseghin et al. (2001, 2003) (that is, 0.419) for non diabetic subjects, with a much higher percentage amongst the females (64.9%).

Insulin resistance generally rises with increasing body fat content (Abbasi et al., 2002; Yeni-Komshian et al., 2000). This was noted as individuals in the IR group had significantly higher mean weight, mean BMI, mean waist and hip circumference (Table 3) compared to NIR group. Furthermore, a higher percentage of IR subjects suffered from abdominal obesity.

The means or medians of almost all biochemical parameters, except for HDL- cholesterol, were significantly higher in the IR group. The identified IR group had all the well recognized characteristics of insulin resistance as diagnosed by the gold standard method. This was also noted when the HOMA index was used for selection, but it was felt that many individuals were missed, particularly the mildly resistant cases, or lean individuals with beta cell dysfunction, especially individuals with mild hyperglycemia. This is a well known draw back of the method (Hanson et al., 2000; Yeni-Komshian et al., 2000). Compared to HOMA I, QUICKI has been reported to have the advantage of being applicable to wider ranges of insulin sensitivity (Ascaso et al., 2001; Hrebicek et al., 2002; Kirwan et al., 2001).

Approximately 88% of individuals identified by the QUICKI were either obese or overweight and 54% suffered from abdominal obesity. However, this group did not have most of the well recognized biochemical characteristics of insulin resistance and their calculated parameters did not significantly differ to those of the NIR group determined by modified QUICKI. Thus, there seems to be an over estimation of insulin resistance when QUICKI is used (22).

Therefore, it can be concluded that the used modified QUICKI has managed to divide the study population into 2 distinct groups differing in their anthropometric and biochemical characteristics and without including or excluding individuals inappropriately, unlike the other 2 indices. The benefits of including FFA into the QUICKI formula can be explained by the following:

i) Increased fasting FFA concentration could reflect insulin resistance earlier than hyperglycaemia since lipolysis is more sensitive to insulin than glucose utilization

(Stumvoll et al., 2002).
ii) A small increase in plasma FFA concentration in healthy individuals is reported to induce insulin resistance (Roden et al., 1996). Insulin sensitivity of lipolysis was suggested to explain about 10% of the variation in insulin sensitivity of glucose disposal in normal subjects (Stumvoll et al., 2002).
iii) Dysfunctional regulation of lipolysis was established In insulin resistant subjects (Groop et al., 1989).
iv.) In fact, modified QUICKI has already been reported to be better correlated with clamp measurement than the original QUICKI or HOMAIR (Perseghin et al., 2001; Rabasa-Lhoret et al., 2003). Even though correlation with the clamp technique was not conducted in this work, the significant difference found between the insulin resistant and the non insulin resistant groups in anthropometric and biochemical characteristics justify our optimism in the ability of this equation to diagnose insulin resistance in our Saudi population. More work should be conducted to find the best cut-off point for diagnosing insulin resistance in different population subgroups according to their BMI or class of obesity. We must also try to verify our results using the clamp technique. Future work should also look at including other measures of lipolysis such as glycerol.

Conclusion

Our results are highly suggestive that by including plasma FFA as a measure of lipolysis in the QUICKI, its power of detecting insulin resistance has certainly been improved, thus, making the modified QUICKI a more powerful diagnostic index of IR in Saudi non diabetic adults.

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