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Original Article

Comparison of insulin resistance by indirect methods - HOMA, QUICKI and McAuley - with fasting insulin in patients with type 2 diabetes in Galle, Sri Lanka: A pilot study

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Abstract:
Background: To investigate importance of fasting insulin (FI) as a diagnostic test for insulin resistance (IR) and to compare with other standard methods McAuley (McA), HOMA and QUICKI indices in Diabetes Mellitus (DM).
Method: 42 diabetic patients who have been already diagnosed were used in our study. They were investigated for fasting blood glucose (FBS), FI, LDL, Triglycerides (TG), total cholesterol (TC) and HDL levels. IR was calculated by McA, HOMA, QUICKI indices and by FI.
Results: 81% of patients were insulin resistant by McA and FI in our study group. 93% were detected as insulin resistant by HOMA and QUICKI. IR by FI was further compared with HOMA and QUICKI and 81% of patients were found to be insulin resistant by FI, HOMA and QUICKI. Results showed that there was a significant correlation between FI and McA in expressing IR in our study group ($p < 0.01$, $r = -0.849$). Further, FI had a statistically significant correlation with HOMA and QUICKI indices ($p < 0.01$, $r = 0.906$ and $p < 0.01$ $r = -0.822$ respectively).
Conclusion: FI measurement alone in diabetic patients has detected IR in 81% of patients, similar to the other standard methods (McA; 81%, HOMA and QUICKI; 93%). We further identified that FI as a diagnostic test of IR had substantial correlation with McA. Our results recommend further studies to see the possibility of taking fasting insulin to determine IR in type 2 diabetic population.
Key Words: Insulin resistance, McAuley index, HOMA index, QUICKI index, Fasting insulin, Type 2 diabetes mellitus.

Introduction:

Insulin resistance (IR) is an important risk factor for type 2 diabetes mellitus (DM).[1] There is evidence to support the fact that by the time glucose tolerance or fasting glucose levels become impaired, appreciable β cell destruction may have already occurred.[2] Early identification of insulin resistant individuals is important for the management strategies of DM. The euglycaemic insulin clamp method, intravenous glucose tolerance test (IVGTT) and minimal model approximation of the metabolism of glucose (MMAMG) are standard methods for the measurement of insulin resistance in research. However, they are impractical in clinical practice and are difficult to perform in population based research studies.[3,4]

In addition to these standard methods, there are indirect methods for the assessment of IR; Homeostasis Model Assessments (HOMA)[5], Quantitative Insulin Sensitivity Check Index (QUICKI)[6], and McAuley index (McA)[7]. HOMA and QUICKI indices are calculated using both the fasting insulin (FI) and fasting blood glucose levels. McA is calculated using fasting insulin and fasting triglyceride level. When confronted with the results obtained by the MMAMG (gold standard method), the sensitivity and specificity of diagnosis were higher by the indirect method as proposed by McAuley.[4] It has been found that, FI is also accurate at predicting IR in the normoglycaemic population similar to HOMA, insulin to glucose ratio and the Bennett index.[7] FI ≥12mu/l have been proposed as the limiting level for IR[7] in non-diabetic population and has been considered as cut off points for diabetic population as well.

A simple, feasible test for identifying insulin resistant individuals is important for both population based research and clinical practice in planning optimal management strategies for patients with DM. Therefore, we hypothesized that, measurement of FI could be used as a more simple, feasible and rapid diagnostic test when compared to other indirect methods of diagnosing IR. Studies related to the FI in determination of IR in patients with DM are limited. Therefore, we assessed the importance of FI as a diagnostic test of IR in recently diagnosed type 2 diabetic patients by analyzing its correlation to IR in comparison to McA, HOMA and QUICKI methods.

Materials and Methods:

Forty two recently diagnosed Type 2 diabetic patients were included in the study from clinics of public and private hospitals. Inclusion criteria of our study were fasting plasma glucose >7 mmol/L (126 mg/dl) in one occasion if the patient is symptomatic, or in two occasions if the patient is asymptomatic. Clinical history was obtained from all patients including age, sex, drugs, smoking, alcohol consumption, level of physical exercise, previous history of diabetes, coronary heart disease and peripheral vascular disease. Family history of diabetes was also ascertained. Following exclusion criteria were used in this study: hypothyroidism, liver, kidney or heart failure and neoplasm. Informed written consent was taken from the selected patients. After 12 hours of overnight fast, each participant's weight, height and blood pressure were measured and recorded. Blood samples were collected into the in dry tubes with EDTA. Plasma was separated immediately by centrifugation at 4000 rpm for a period of 10 minutes. Fasting blood glucose was assessed by absorbance method (Diagnostica- Merck). Fasting insulin was assessed by ELISA (Diagnostic-Automation). Fasting triglyceride levels were measured enzymatically by colorimetric test (LABKIT). Four indirect methods used for the assessment of IR were calculated using the equations mentioned below.

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

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

QUICKI = 1/(log insulin+log glycemia in mg/dL)

Patients were considered as insulin resistant when McA ≤5.8, HOMA ≥2.6 and QUICKI ≤0.33.[7,8] Fasting insulin was considered to assess IR and FI level ≥12mU/l was considered as insulin resistant among both non-diabetic and diabetic (<15mU/l) populations.[7-9]

Statistical analysis: For the descriptive statistics after having checked the normality of the variables using the Kolmogorov-Smirnov test, the usual central and dispersion methods were used: average, SD, and 95% CI. The statistical significance of differences between the means were evaluated using the paired Student's T-test in the case of normal distribution of data sets, and using the Kolmogorov-Smirnov test when at least in one of the data sets the normal distribution was excluded. The sensitivity and specificity of insulin resistance indexes were estimated as true-positive results/(true-positive results + false-negative results) and true-negative results/(true-negative results + false-positive results), respectively. Sensitivity showed the ability to detect insulin resistance by doing fasting insulin alone when patients are really insulin resistant by the gold standard method. Specificity detected the ability to as insulin sensitive when the patients are really insulin sensitive by the gold standard. Cohen's kappa was used to check the validity of FI as a diagnostic test to determine the IR. Correlation between two variables was studied with the Spearman rank-order. All statistical analyses were performed using Microcal origin 4.1 and Microsoft Excel whenever applicable.

Results:

1.1. Baseline characteristics and prevalence of IR in our study group:

Table 1 shows the mean values of weight, BMI, fasting insulin, fasting blood glucose, McA, HOMA and QUICKI of our study group.

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

Characteristics	Mean±SEM
Age (years)	46±1.6
BMI (kg/m^2)	23.7±0.6
Total cholesterol (mg/dL)	248.2±7.6
Triglycerides (mg/dL)	158.0±6.1
HDL Cholesterol (mg/dL)	57.5±1.6
LDL cholesterol (mg/dL)	158.2±7.6
Fasting blood glucose (mg/dL)	179.3±10.2
Fasting insulin (mU/L))	38.8±4.7
McAuley Index	4.8±0.2
HOMA Index	18.1±2.51
QUICKI Index	0.28±0.005

Values given as mean±SEM

Table 1 shows the mean values of weight, BMI, fasting insulin, fasting blood glucose, McA, HOMA and QUICKI of our study group.

Our results show that 39 out of 42 patients (93%) were insulin resistant by HOMA and QUICKI (Figure 1). 34 out of 42 patients (81%) were insulin resistant by McA and 34 out of 42 patients (81%) were found to be IR by FI test in all patients (Figure 1).

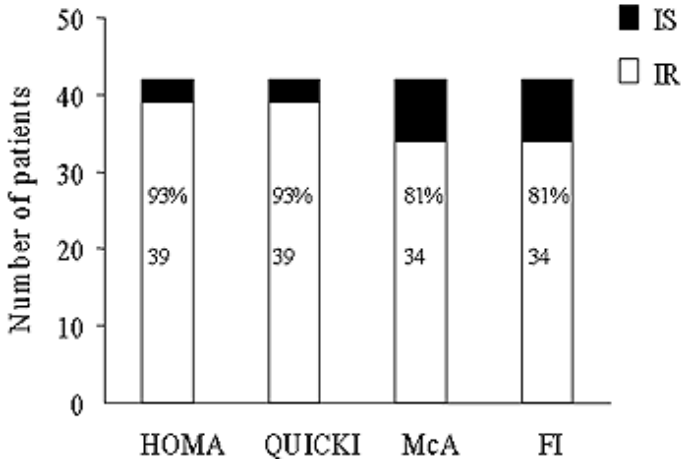

Figure 1 - Insulin resistance among type 2 diabetes mellitus by indirect methods.
Figure shows the number and percentage of patients who are insulin resistant by FI, McA, HOMA and QUICKI indices. 34 of 42 (81%) patients are IR by FI and McA indices. 39 out of 42 (93%) patients are IR by HOMA and QUICKI indices. IR - Insulin Resistant; IS - Insulin Sensitive

Out of 34 patients who were insulin resistant by McA, 32 patients (94%) were detected to be insulin resistant by FI (Figure 2A). Out of 39 patients who were insulin resistant by HOMA and QUICKI, 34 patients (87%) were detected to be insulin resistant by FI (Figure 2B, 2C).

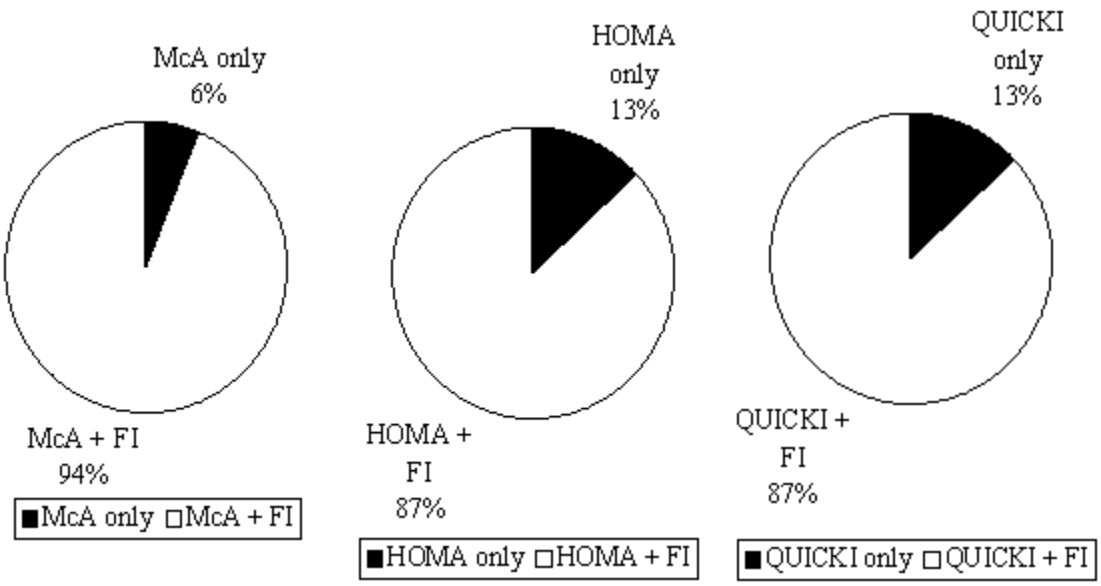

Fig. 2 – Sensitivity of insulin resistance by fasting insulin test in comparison to McA, HOMA and QUICKI.

This figure shows sensitivity of detecting IR by FI when compared to McA, HOMA and QUICKI indices. [A]- Out of the patients who had IR by McA 94% of them were detected having IR by FI and only 6% of them were unable to detected by FI. [B] and [C]- Out of the patients who were IR by HOMA and QUICKI indices 87% of them were detected having IR by FI. 13% of them were unable to detect by FI.

1.2. Statistically significant correlation of FI test with McA, HOMA and QUICKI

FI and McA methods detected similar number of patients with IR in our study group. Therefore, we investigated the significance of correlation coefficient between FI and other indirect indices in detecting IR. Our results showed that correlation between FI test with McA (95% CI, $r = -0.85$, $P < 0.01$) was statistically significant [Figure 3(i)). Correlation coefficient of FI with HOMA (95% CI, $r = 0.91$, $p < 0.01$) and QUICKI (95% CI, $r = -0.82$, $p < 0.01$) also had significant correlations (Figure 3(ii), 3(iii)].

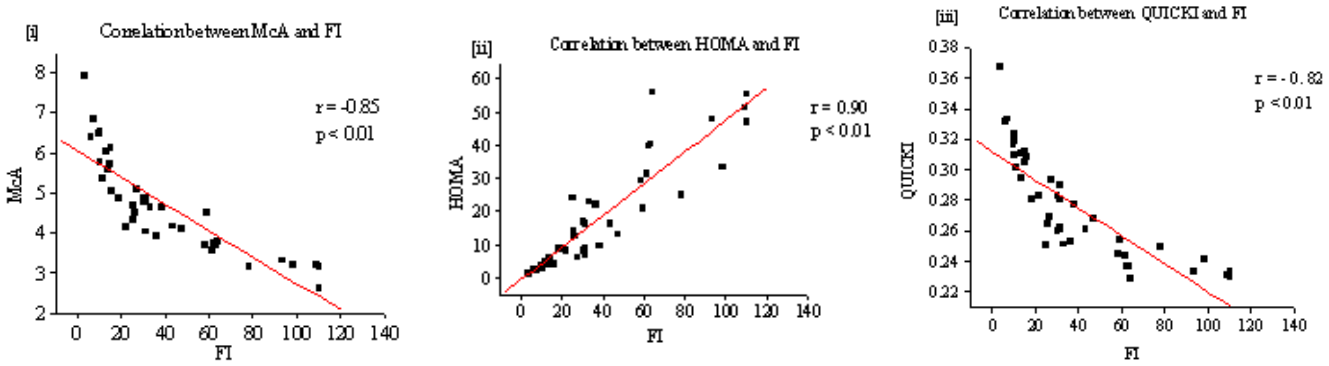

Fig.3 – Correlation between fasting insulin with McA, HOMA and QUICKI in detecting insulin resistance.

This figure shows the correlation between FI with McA, HOMA and QUICKI indices. [i]-The correlation of FI with McA is statistically significant ($r = -0.849$, $p<0.01$). [ii]-The correlation between FI and HOMA is statistically significant. ($r=0.906$, $p<0.01$). [iii]-The correlation of FI with QUICKI is also statistically significant ($r=0.82$, $p<0.01$).

Sensitivity and specificity of fasting insulin as a diagnostic test in comparison to McA, HOMA and QUICKI:

We further analyzed the specificity and sensitivity of FI as a diagnostic test by comparing it with standard tests; McA, HOMA and QUICKI in this study. We found that FI test had 94% of sensitivity and 75% of specificity when compared with McA. FI test had 87% of sensitivity and 100% of specificity when compared to HOMA & QUICKI. Validity of FI as a diagnostic test of IR was further analyzed by Cohen's kappa test. FI had a substantial agreement ($k=0.7$) when compared to McA, and moderate agreement ($k=0.5$) with HOMA as well as QUICKI (Table 2).

Table 2: Sensitivity and specificity of fasting insulin as a diagnostic method of insulin resistance in comparison to McA, HOMA and QUICKI

	MCA	HOMA	QUICKI
Sensitivity	94%	87%	87%
Specificity	75%	100%	100%
kappa	0.7	0.5	0.5
Agreement	Substantial	Moderate	Moderate

Discussion:

The goal of this study was to identify another reliable simple method for the detection of IR, other than McAuley, HOMA and QUICKI indices. We analyzed diabetic patients who were diagnosed within 6 months so as to deal with early changes in IR among them. They were analyzed the correlation of McA, HOMA and QUICKI with FI test in diagnosing IR. Out of the patients who were resistant by McA 94% of them were resistant by FI and only 6% of them were unable to be detected by FI test. According to the previous research, McA is the most accurate indirect method of detecting IR and when confronted with the results obtained by the MMAMG, the sensitivity and specificity of diagnosis were also higher by McA.[4] It has been already found that FI test is accurate at predicting IR in normoglycaemic population[7] and we also show that FI test in diabetic patient can significantly detect the IR similar to McA. Out of the patients who had IR by HOMA and QUICKI indices, only 87% were detected

having IR by FI test. 13% of patients who were detected by HOMA and QUICKI were not detected by FI. This can be explained by limitations that were found out with HOMA and QUICKI with other researchers. One limitation is that HOMA is calculated from fasting glucose and fasting insulin and thereby reflects only hepatic insulin sensitivity.[10] Results of the Miyazaki's group facilitate these findings by studying the composite insulin resistance, which includes both hepatic and peripheral resistance for the assessment of insulin sensitivity in diabetic patients.[12] Therefore, considering all the factors we hereby suggest that FI is sensitive and also specific as McA in assessment of IR in diabetic population. Our results are in agreement with results obtained by Louise S.C[9] et al showing that significant negative correlation between HOMA-IR and sensitivity (S) (r = -0.89, r = -0.90, and r = -0.81, P <0.01) and a significant positive correlation between QUICKI and S (r = 0.89, r = 0.90, and r = 0.81, P <0.01) at each time point. They suggested that HOMA-IR, QUICKI and fasting insulin correlate strongly with S assessed by the FSIVGTT (frequently sampled intravenous glucose tolerance test) in obese children and adolescents.[9]

In addition, the correlations of FI with McA, HOMA and QUICKI are significant ($p < 0.01$). We also found that FI test had significant sensitivity and specificity when compared to McA, HOMA & QUICKI indices. This observation suggests that assessment of IR by FI gives parallel results to the assessment of IR by other methods. Validity of FI was further analyzed by Cohen's kappa test and had a satisfactory agreement ($k = 0.7$). All together, suggest that FI can be used as an easy test to detect IR also in diabetic population. We also would like to draw your attention on our minor failures, in our study plan. Because our study sample is small, our results might not predict values in population based research in diabetes. Therefore, we would like to draw an attention on population based studies for assessment of sensitivity and specificity of this FI test prior to the recommendation for clinical practice.

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