The Ideal Insulin Resistance Index for Cardiovascular Risk Discrimination in type 2 Diabetes Mellitus

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Research Article

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Abstract

Background

This study was aimed at determining the correlation between insulin resistance indices and atherogenic index as well as determining the ability of the indices to discriminate between low and high cardiovascular risk in diabetic individuals. The study involved 70 participants. Ethical approval was granted by the institution review board. Fasting plasma glucose, insulin and lipid profile were analyzed for each participant. Atherogenic index of plasma (AIP), homeostatic mode assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), fasting glucose insulin ratio (FIR), fasting insulin resistance index (FIRI), McAuley's index and Raynaud's index were calculated using the appropriate formulae. Pearson's correlation and receiver operating characteristic (ROC) analysis were done.

Results

The mean age of the participants was 53.34 ± 9.57 years. Males were 50%. The mean duration of type 2 diabetes in the participants was 6.29 ± 2.78 years. Each index had a strong and significant correlation with fasting plasma insulin ($p < 0.001$). Using AIP as a marker of cardiovascular risk, 14.3% had intermediate/high risk. Among the indices, only McAuley's index showed a statistically significant negative correlation with AIP ($r = -0.453; p < 0.001$). None of the indices could reliably discriminate between low and intermediate/high cardiovascular risk.

Conclusion

The studied indices could not predict cardiovascular risk despite their usefulness as insulin resistance markers. Further studies are needed to identify an ideal insulin resistance index that can also predict cardiovascular risk.

Background

Insulin is a peptide hormone produced by the beta cells of the pancreatic islets of Langerhans and binds to a membrane-bound receptor, the insulin receptor, to elicit the appropriate metabolic and mitogenic effects.¹ Insulin resistance is the attenuated biological response to insulin.² Insulin resistance is central to the pathogenesis of type 2 diabetes mellitus especially in the presence of beta cell dysfunction which causes the inability of the beta cells to compensate for the insulin resistance.³ Insulin resistance is not only a risk factor to type 2 diabetes but also a dominant theme in a concurrent constellation of cardiovascular risk factors such as hypertension, dyslipidaemia, central obesity and glucose intolerance, a condition termed metabolic syndrome or insulin resistance syndrome.⁴

Cardiovascular disease is the commonest cause of mortality in both developed and developing countries.⁵ Cardiovascular risk estimation is imperative to preventing cardiovascular mortality through

the modification of cardiovascular risk factors.⁶ However, most of the cardiovascular risk calculators are cumbersome, complicated and require special software making them impracticable in clinical practice especially in low resource settings. Also, it has been documented that risk estimation is not consistent across the risk calculators.⁷ Considering these drawbacks, atherogenic index of plasma (AIP) is a simplified and optimal indicator of cardiovascular risk and it obviates most of the challenges associated with cardiovascular risk calculators.^{8,9} Previous studies have validated AIP as a reliable biomarker of the risk of atherosclerotic cardiovascular disease.^{10–12}

Insulin resistance is an independent cardiovascular risk factor.¹³ Clinically, it is technically difficult to measure insulin resistance. The gold standard tool for estimating insulin resistance is the hyperinsulinaemic euglycaemic clamp but it is time and resource-intensive and not clinically useful.¹⁴ There are several indices, documented in the literature, that are used as estimates of insulin resistance. These indices are divided into two categories- dynamic indices and basal indices.^{15,16}

Dynamic indices are derived from glucose tolerance tests and repeated blood sampling which makes them unsuitable for routine day-to-day clinical practice.¹⁵ Examples of these are Matsuda's, Belfiore's, Avignon's, Strumvell's and Gutt's index. The basal indices, on the other hand, require one-time sampling, usually fasting, for metabolites such as insulin, glucose and triglyceride.¹⁵ Examples of these are the homeostatic mode assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), fasting glucose insulin ratio (FGIR), fasting insulin resistance index (FIRI), McAuley's index and Raynauld's index. The basal indices are suitable for clinical practice but there is paucity of data on which one of them gives optimal information about the cardiovascular risk of individuals living with type 2 diabetes mellitus.

Aim

The aim of the study was to assess the correlation between insulin resistance indices and atherogenic index and to determine the ability of the indices to discriminate between low and high cardiovascular risk in diabetic individuals

Methods

The study involved 70 individuals (35 males and 35 females) previously diagnosed with type 2 diabetes mellitus and who were attending the outpatient diabetes clinic of a major referral hospital in Southern Nigeria. The hospital's ethical committee gave the ethical approval for the study. Additionally, the participants gave written informed consent before they were allowed to participate in the study. Exclusion criteria were insulin administration, recent acute metabolic decompensation, pregnancy, use of drugs like steroids and anti-psychotic medications and hospital admission in the preceding 3 months.

Participants fasted overnight for 8–12 hours. Thereafter, samples were collected for fasting insulin, fasting plasma glucose and fasting lipid profile. Total cholesterol, triglycerides (TG) and high density lipoprotein-cholesterol (HDL-C) were analyzed using enzymatic method and run on Landwind C100plus AutoChemistry Analyzer. Fasting plasma glucose (FPG) was analyzed using enzymatic method and run on Landwind C100plus AutoChemistry Analyzer. The intra-assay and inter-assay coefficients of variation for FPG were 2.98% and 3.02% respectively. Fasting plasma insulin was measured by enzyme-linked immunosorbent assay (ELISA) using Cell Biolab Human Insulin ELISA kit. The intra-assay and inter-assay coefficients of variations were 4.83% and 5.74% respectively. Glycated haemoglobin (HbA1c) was determined using high performance liquid chromatography method. Coefficient of variation was 1.74%.

Insulin resistance indices (HOMA-IR, QUICKI, FIGR, FIRI, McCauley's index and Raynaud's index) as well as AIP were calculated using the appropriate formulae as shown below.^{10,15} AIP > 0.11 was taken as intermediate to high cardiovascular risk.¹²

The data collected were scrutinized for errors as soon as collected. They were coded and entered into Microsoft Excel datasheet before they were transferred for data analysis. Data analysis was carried out using the Statistical Package for Social Sciences software (SPSS) version 22 (IBM, New York, USA). Quantitative variables were presented as mean $\pm$ standard deviation (SD). Correlation was done with Pearson's correlation. Receiver operating characteristic (ROC) analysis was done and the area under curve (AUC) was determined with 95% confidence interval (CI). AUC of 0.5–0.7 and > 0.7 were considered as weak and strong predictors of cardiovascular risk category respectively. *P* value < 0.5 is considered statistically significant.

FPG in mmol/L was converted to mg/dl by multiplying with 18

TG in mmol/L was converted to mg/dl by multiplying with 88.5

$$\text{AIP} = \text{Log} \left(\frac{\text{TG (mmo/L)}}{\text{HDL-C (mmo/L)}} \right)$$

$$\text{FIRI} = \frac{\text{Fasting insulin (}\mu\text{mol/L)} \times \text{FPG (mmo/L)}}{25}$$

$$\text{FGIR} = \frac{\text{FPG (mmo/L)}}{\text{Fasting insulin (}\mu\text{mol/L)}}$$

$$\text{HOMA-IR} = \frac{\text{Fasting insulin (}\mu\text{mol/L)} \times \text{FPG (mg/dl)}}{22.5}$$

$$\text{McCauley's index} = \frac{1}{e^{[2.63 - 0.28 \ln(\text{fasting insulin}) - 0.3 \ln(\text{TG mmo/L})]}}$$

$$\text{QUICKI} = \frac{1}{\text{Log (Fasting insulin } \mu\text{mol/L)} + \text{Log (FPG mg/dl)}}$$

$$\text{Raynaud's index} = \frac{40}{\text{Fasting insulin (}\mu\text{mol/L)}}$$

Results

There were 70 participants with equal male and female distribution. The mean age of the participants was 53.34 ± 9.57 years. The mean duration of type 2 diabetes in the participants was

6.29 ± 2.78 years. Table 1 shows the baseline characteristics of the patient. Table 2 shows the correlation between AIP and the insulin resistance indices (FIRI, HOMA-IR, McAuley's index, QUICKI and Raynaud's index). There was a strong and statistically significant correlation (all had $p < 0.001$) between fasting plasma insulin and all insulin resistance indices. Among the indices, only McAuley's index showed a statistically significant correlation with AIP ($r = -0.453; p < 0.001$). The correlation between McAuley's index and AIP is depicted on Fig. 1.

Figure 2 shows the risk stratification of the participants, using AIP as a cardiovascular risk marker. Ten (14.3%) participants were in the intermediate/high risk category while the other participants were in the low risk category. Figure 3 shows ROC curves of the insulin resistance indices using AIP cardiovascular risk categories (low and intermediate/high risk categories) as the binary responses. Table 3 shows the AUC of each index. None of the indices is a strong discriminator of cardiovascular risk. In spite of this, QUICKI had the highest AUC. At a cut-off value of 0.33,¹⁵ the sensitivity and specificity of QUICKI in predicting cardiovascular risk category were 80% and 50% respectively

Table 1
Baseline characteristics of the participants

Parameter	Mean	SD
FPG (mmol/L)	6.32	0.87
Fasting plasma insulin (μ mol/L)	9.41	0.38
HbA1c (%)	6.98	0.72
TG (mmol/L)	1.15	0.19
HDL-C (mmol/L)	1.28	0.31
AIP	-0.04	0.14
FIRI	42.30	13.34
FIGR	13.56	5.25
HOMA-IR	2.64	0.91
McAuley's index	7.26	0.72
QUICKI	0.33	0.01
Raynaud's index	4.70	0.22

Table 2
Correlation between AIP and insulin resistance indices.

Insulin resistance index	r	P
FIGR	-0.170	0.158
FIRI	0.087	0.474
HOMA-IR	0.048	0.691
McAuley's index	-0.453	0.000**
QUICKI	-0.116	0.340
Raynaud's index	-0.175	0.148
r- Pearson's correlation coefficient		
** - statistically significant		

Table 3
AUC of the insulin resistance indices

Index	AUC	95% Confidence interval		<i>p</i>
FGIR	0.530	0.327	0.733	0.763
FIRI	0.437	0.270	0.605	0.529
HOMA-IR	0.437	0.270	0.604	0.524
McAuley's index	0.317	0.158	0.475	0.065
QUICKI	0.563	0.395	0.730	0.529
Raynaud's index	0.540	0.352	0.728	0.687

Discussion

The participants were mostly middle-aged. The onset of type 2 diabetes mellitus usually falls in this age group as reported from previous studies.^{17,18} This is partly due to the increased prevalence of the risk factors for diabetes such as obesity, hypertension, physical inactivity and dyslipidaemia in this age group.¹⁸ Going by the mean FPG and the HbA1c, it can be deduced that the short term and long term glycaemic control are averagely good. The participants were being managed at a tertiary hospital where the best of diabetes care is offered so, attaining good glycaemic control may be unsurprising. Moreover, it can also be assumed that since their anti-diabetic medications required to achieve optimal glycaemic control did not require insulin (an exclusion criterion), the metabolic control must have been within acceptable limit.

Fasting plasma insulin has been used as an indicator of insulin resistance in previous studies.^{19–21} This study, unsurprisingly, found a strong and statistically significant correlation between all the studied indices (FIGR, FIRI, HOMA-IR, McAuley's index, QUICKI and Raynaud's index) and fasting plasma insulin. All the indices have fasting plasma insulin in their formulae and this can explain the strong correlation. Antoniolli *et al*, in their study, have also affirmed that all the insulin resistance indices studied in this research have been extensively studied and validated as reliable markers of insulin resistance.¹⁵ So, the usefulness of indices as markers of insulin resistance is established but whether they could predict cardiovascular risk has been the bone of contention.

Using AIP as a marker of cardiovascular risk, 14.3% of the participants fell within the high/intermediate cardiovascular risk category. This may be explained by their good glycaemic control and the absence of markedly deranged lipid profile. AIP is mainly derived from the mathematical transformation of fasting TG and HDL-C and since this study showed acceptable TG and HDL-C profile, it may be unsurprising that the vast majority of the patients were within the low cardiovascular risk category.¹⁰ This present study,

being a hospital-based study, may however not reflect what is found in the general population living with diabetes in the community.

Moreover, since insulin resistance is an independent cardiovascular risk factor, one would expect that indices of insulin resistance to correlate with a validated marker of cardiovascular risk such as AIP. Surprisingly, as demonstrated in the present study, only McAuley's index significantly correlated with AIP. All the other insulin resistance indices (FIGR, FIRI, HOMA-IR, QUICKI and Raynaud's index) did not attain statistically significant correlation with AIP. Similar to the findings of this present study, some authors, working in Pakistan, could not demonstrate any statistically significant correlation between indices of insulin resistance and cardiometabolic risk factors among individuals living with type 2 diabetes mellitus.²²

Although none of the indices was a strong predictor of cardiovascular risk category yet, QUICKI had the largest AUC which suggests that it had the highest ability to discriminate between individuals with low and intermediate/high cardiovascular risk. It is however worthy of note that this discriminatory power did not attain statistical significance. In a cohort of patients with polycystic ovarian syndrome, Wanderley *et al*/reported an association between some cardiovascular risk factors and QUICKI.²³ However, their study was not centred around individuals living with type 2 diabetes mellitus.

Limitations

The sample size could have been larger to demonstrate the relationship among the variables better. Similarly, a community-based, rather than hospital-based, approach might be a better alternative so as to capture the whole spectrum of diabetic participants in their usual state unlike the vastly well controlled type 2 diabetes patients involved in this study.

Conclusion

This study demonstrated that FIGR, FIRI, HOMA-IR, McAuley's index, QUICKI and Raynaud's index correlated strongly with fasting plasma insulin (a validated biomarker of insulin resistance) in a cohort of individuals with type 2 diabetes and may therefore be reliably used to determine insulin resistance in such people. However, none of these indices could reliably discriminate between low and high cardiovascular risk. Newer markers of insulin resistance that can also predict cardiovascular risk would be needed especially in people living with diabetes mellitus.

Abbreviations

AIP - Atherogenic index of plasma

AUC – Area under curve

CI – Confidence interval

ELISA - Enzyme-linked immunosorbent assay

FGIR - Fasting glucose insulin ratio

FIRI - Fasting insulin resistance index

FPG – Fasting plasma glucose

HbA1c - Glycated haemoglobin

HDL-C - High density lipoprotein-cholesterol

HOMA-IR - Homeostatic model assessment of insulin resistance

QUICKI - Quantitative insulin sensitivity check index

ROC - Receiver operating characteristic

SPSS - Statistical Package for Social Sciences software

TG – Triglyceride

Declarations

Ethical approval and consent to participate:

Ethical approval was granted by the ethical committee of the Institute Advanced Medical Research and Training with the reference number NHREC/05/01/2008a. The ethical approval number for the study was UI/EC/17/0284. Also, the recruited participants gave written informed consent to partake in the study.

Consent for publication:

was taken from all participants.

Availability of data and material:

Available, if required.

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Competing interest:

None.

Authors' contribution statement:

TA had the research conception and did the research design, data collection, data analysis, writing and editing of the manuscript. I have read the manuscript again and I approve its submission.

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Figures

Figure 1

Correlation between McAuley’s index and AIP

Figure 2

Cardiovascular risk categories of the participants

Figure 3

ROC curves of the insulin resistance indices