Research Paper

Comparison of McAuley/fasting insulin indices with ATP III clinical criteria for the diagnosis of insulin resistance in type 2 diabetes mellitus

Hettihewa L. M., Weerarathna T. P[1]

Departments of Pharmacology and [1]Medicine, Faculty of Medicine, University of Ruhuna, Sri Lanka

ABSTRACT

Objective: To estimate the prevalence of insulin resistant syndrome (IRS) among newly diagnosed patients with type 2 diabetes and to test their validity against two indices of insulin resistance (IR). **Materials and Methods:** Prevalence of IRS was estimated according to the criteria used by ATP III in newly diagnosed type 2 diabetic patients. Sensitivity and specificity of the ACE criteria were calculated against two indices of IR namely fasting insulin (FI) level > 12 mU/l and McAuley index (McA) < 5.8. [McA= exp [2.63--0.28 ln(insulin in mU/l) -- 0.31 ln(triglycerides in mmol/l)]. **Results:** 35.7% of patients had IRS by ATP III criteria. 64.3% of patients were insulin resistant by FI and McA in each index. In patients who had IRS with ATP criteria, 80% and 86.6% were found to have McA and FI in the insulin resistant range. Out of the patients who were resistant by McA, only 40.6% had IR by ACE criteria and 93% had shown IR by FI. Out of all patients who did not fulfill the ATP III for IR, 74% and 59% were detected as having IR by fasting insulin and McA respectively. Sensitivity of the ACE criteria when tested against the FI and McA were 37.5% and 40.6%, specificity were 70% and 80%, respectively. **Conclusions:** IRS was common among the newly diagnosed patients with type 2 diabetes. ACE criteria showed an acceptable specificity but lack adequate sensitivity when compared with the two Indices of insulin resistance. More valid and clinically useful criteria should be available for the accurate diagnosis of IRS in clinical practice.

Key words: ATP III criteria, insulin resistance, McAuley index, type 2 diabetes

INTRODUCTION

Incidence of type 2 diabetes is reaching epidemic proportions globally, particularly in the South Asian region.[1] Etiologically, type 2 diabetes is characterized by the presence of insulin resistance and relative insulin deficiency.[2] The insulin resistance syndrome (IRS) describes a condition that is characterized by decreased tissue sensitivity to the action of insulin, leading to a compensatory increase in insulin secretion.[3] This metabolic dysfunction leads to a cluster of abnormalities with serious clinical consequences, most importantly, cardiovascular disease and/or type 2 diabetes.[3]

The risk factors an individual has, the greater the likelihood of having the insulin resistance syndrome are overweight: A body mass index (BMI) ≥ 25 kg/m^2 or a waist circumference of >40 in. for men and >35 in. for women, sedentary lifestyle, over age 40 years, non-Caucasian ethnicity, family history of type 2 diabetes, hypertension or cardiovascular disease, history of glucose intolerance or gestational diabetes, diagnosis of hypertension, elevated triglycerides/low HDL-cholesterol, or cardiovascular disease, acanthosis nigrican[5] and polycystic ovary syndrome.[3-6]

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.83280

Address for correspondence:
Lukshmy M. Hettihewa, Department of Pharmacology, Faculty of Medicine, University of Ruhuna, Sri Lanka. E-mail: menik@med.ruh.ac.lk

The third adult treatment panel (ATP) III, under the auspices of the National Cholesterol Education Program (NCEP), has revised its guidelines for cholesterol testing and management. This evidence-based set of guidelines builds on ATP I (1988) and ATP II (1993), and expands the indications for intensive cholesterol-lowering in clinical practice.

The euglycemic insulin clamp and the intravenous glucose tolerance test are gold standard methods for measurement of insulin resistance in research, but they are impractical in clinical practice and are difficult to perform in population-based research studies.[7-10] In addition, three indirect indices for the assessment of insulin resistance (IR) are HOMA index[11,12] [insulin (μU/ml) X glucose (mmol/L)/22.5], QUICKI index[13,14] [1/log insulin + log glycemia in mg/dl) and McAuley index:[15] [McA = exp(2.63-0.28 ln(insulin in mU/l) – 0.31ln(triglycerides in mmol/l)]. Cut-off points of fasting insulin and McAuley index (McA) for insulin resistance are 12 mIU/l[14] and ≤ 5.8, [11] respectively. The most commonly used criteria in the United States are those of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III).[3,16] These include obesity- both global and central (waist circumference of more than 102 cm in men or more than 88 cm in women), serum triglycerides, serum HDL cholesterol, and blood pressure [Table 1].[6]

The American College of Endocrinology recently described IRS as the constellation of more than three of the above criteria in a single individual.[3,15] According to this classification, an individual with type 2 diabetes can be classified as having IRS when he has more than two of the criteria other than elevated blood glucose. The Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) (ATP III) (2001 and 2004) laid down clinical criteria for diagnosis of insulin resistance syndrome, and it included the following.

BMI of 25 kg/m^2 or higher, triglyceride level of 150 mg/dl or higher, HDL-C level of less than 40 mg/dl in men or less than 50 mg/dl in women. Blood pressure of 130/85 mmHg or higher, glucose level of more than 140 mg/dl at 2 h after administration for 75 g of glucose, fasting glucose level of 110–126 mg/dl.

Table 1: IRS classification criteria based on the NCEP/ATP III Guidelines by American College of Endocrinology

Plasma glucose	
Fasting	>110 mg/dl
Impaired fasting glucose	> 100 mg/dl
Triglycerides	> 150 mg/dl
HDL cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	> 130/>85 mm Hg

The ATP III criteria use fasting glucose level as the only measurement of glucose tolerance, while the WHO and AACE criteria include the option of performing a 2-h oral glucose tolerance test (OGTT). Considering different types of diagnosing criteria for insulin resistance we hypothesized to compare and investigate validity of the clinical diagnostic criteria with the indirect IR tests.

There are some research works showing that there is a significant association between cardiovascular morbidity and mortality with metabolic syndrome.[17] Some of the research shows that lots of other biochemical parameters had been tested to assess the insulin resistance.[18,19]

Objectives

Our study is to estimate the prevalence of IRS using ATP III criteria [Table 1] in a cohort of recently diagnosed patients with type 2 diabetes and to compare its sensitivity and specificity with calculated IR by McA and fasting insulin (FI).

MATERIALS AND METHODS

Minimum required number of forty two patients with type 2 diabetes was followed up in the study from private sector. The protocol for this study was approved by the ethical committee of Faculty of Medicine, University of Ruhuna. Informed consent was taken from all patients prior to the recruitment to the study. Clinical history was obtained from all subjects, including age, sex, and intake of 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: age outside the range of 20-65, diabetic patients who were on insulin therapy, hypothyroidism, liver, kidney or heart failure and neoplasm. After 12 h of overnight fast, each participant's weight and height was measured and recorded. Blood pressure was measured in a sitting position after 10 min rest. Body mass index (BMI) was calculated using height (m^2) and weight (kg). Blood samples were collected and deposited in dry tubes. The plasma was separated immediately using centrifugation at 4000 r/min for a period of 10 min. Fasting blood glucose was assessed by absorbance method (Diagnostica- Merck). Plasma insulin was determined by ELISA (Diagnostic-Automation). Fasting triglyceride levels were measured enzymatically by colorimetric test (LABKIT). All analyses were carried out in Molecular Science and Biomedical Unit of the Department of Pharmacology in the Faculty of Medicine, Galle.

Two indirect indices for the assessment of insulin resistance were considered. The IR index, described by McAuley*et al.*[14] based on the increase of plasma triglyceride and insulin, using the equation as mentioned above, was calculated. Subjects with

McA ≤5.8 were considered as insulin resistant. Second method of assessing IR was fasting insulin and its level ≥μU/ml has been considered as insulin resistant.

STATISTICS

For the descriptive analysis, and after having checked the normality of variables the usual central and dispersion methods were used: Mean and standard error of mean (SEM). Sensitivity and specificity were calculated. All statistical analysis were performed using Microcal Origin 4.1 graphic software and Microsoft Excel whenever applicable. Cohen's kappa was used to check the validity of fasting insulin level as a diagnostic test to determine the insulin resistance.

RESULTS

Table 2 shows the characteristics of study sample. Means of fasting insulin and fasting blood glucose levels were 37.9 ± 4.83 μU/ml and 182.93 ± 9.91 mg/dl, respectively.

A total of 35.7% of patients were insulin resistant by criteria laid down by ATP III, 64.3% of them were insulin resistant by fasting insulin levels and McA indices in the resistant range.

Of all the patients who had insulin resistance by criteria laid down by ATP III, only 80% and 86.6% were resistant by McA and fasting insulin respectively [Figure 1].

Out of all patients who did not fulfill the criteria laid down by ATP III for IRS, 74% and 59% were detected as having insulin resistance by fasting insulin and McA, respectively [Figure 2].

Out of the patients who were resistant by McA, only 41% of them had IRS by ATP III criteria and 94% had IRS detected by FI index**.** Therefore we assessed the sensitivity and specificity of criteria by ATP as a diagnostic method of insulin resistance compared to McA and FI indices. Criteria by ATP had 40.6% and 37.5% sensitivity when compared to McA and FI, respectively. In addition, it had 80% and 70% of specificity when compared to McA and fasting insulin, respectively.

Table 2: Baseline parameters

Parameter	Mean ± SEM
Wt (kg)	58.5 ± 1.63
BMI (kg/m^2)	23.6 ± 0.59
FI (μU/ml)	37.9 ± 4.83
FBS (mg/dl)	182.93 ± 9.91
BP (mmHg)	
SBP	124 ± 1.87
DBP	82 ± 1.5

Values are mean ± SEM; n=42

We further assessed the validity of criteria by ATP III as a diagnostic test of IR by Cohen's Kappa test. Data in Table 3 show that criteria by ATP III and McA diagnostic index have no satisfactory agreement (k = 0.13) and the criteria by ATP III and FI diagnostic index have no satisfactory agreement (k = 0.047).

DISCUSSION

The goal of this study was to identify a reliable yet simple method for detection of insulin resistance syndrome in the community. Predicting insulin resistance is important in diabetic population in planning optimal management strategies for the patients with type 2 diabetes. A number of clinical and metabolic abnormalities have been associated with insulin resistance.[7,8] The metabolic disorders were classified as dyslipidemia, hypertension, and impaired glucose tolerance. Howard *et al*[11,12] compared several alternative methods for measuring insulin sensitivity to predict cardiovascular risk.

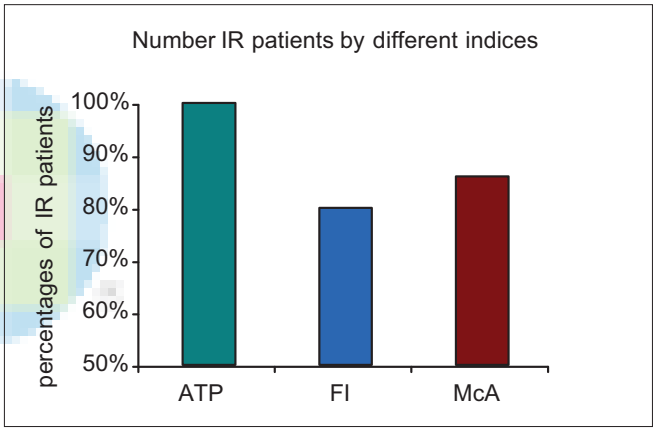

Figure 1: Percentage of insulin resistant patients detected by ATP III criteria was again tested by FI, McA indices. Data shows that only 80% and 86% of patients were positive by FI and McA, respectively

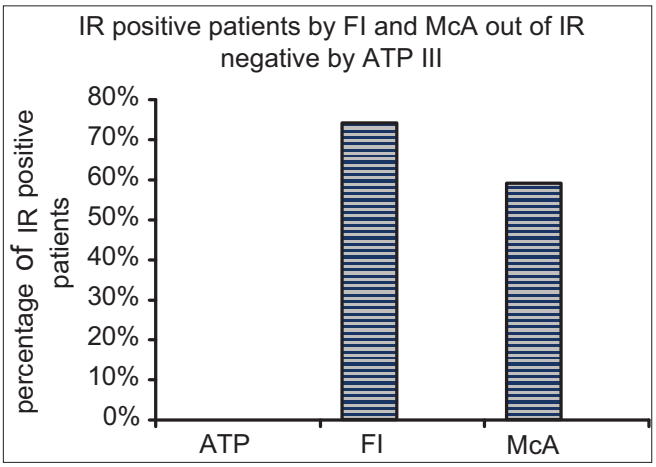

Figure 2: Percentage of positive patients detected by FI and McA indices from the patients who did not fulfill criteria laid down by ATP III for IRS

Table 3: Sensitivity, specificity, and degree of agreement

	Sensitivity (%)	Specificity (%)	Kappa value	Degree of agreement
ATP vs McA	40.62	80	0.130	Slight (0.05--0.29)
ATP vs FI	37.50	70	0.047	Fair (0.30--0.49)

Sensitivity (13/32*100= 40.62%), specificity (8/10*100 = 80%) and the Cohan's kappa (I_o--I_e/1--$I_e I_o$ = observed frequency [(a+d)/42], I_o = 0.5, I_e = expected frequency [(a+b) (a+c) + (b+d) (c+d)/42^2], I_e = 0.13) for the ATP III, McA. These data further shows the FI/ATP III comparison by sensitivity (12/32*100=37.5%), specificity (7/10*100 = 70%) and to check the validity: Cohan's kappa (k = I_o--I_e/1--$I_e I_o$ = 0.452, I_e = 0.47). ATP: adult treatment panel, McA: McAuley index, FI: Fasting insulin.

Many of the methods, including the modified Galvin method and other methods based on the frequently sampled intravenous glucose tolerance test, are invasive and time consuming, and they are not appropriate for general population screening and clinical practice. Even simple indirect methods for diagnosing IR as HOMA index, QUICKI index, McAuley index and fasting insulin level are not readily available for patients in developing countries. Readily available easily measurable clinical and biochemical markers have very important diagnosing value in developing countries.

In present study, we investigated the presence of IR in recently diagnosed diabetic patients using indirect indices and criteria by ATP III.[3] The indirect indices (McA and FI) have high validity of diagnosing IR compared to more approved invasive methods.[11,14] One limitation in the measurement of fasting insulin is an overlap between insulin resistant individuals and normal individuals. Another limitation of this test is the lack of standardization and differences between labs. If the assay for fasting insulin was reliable, it would be useful to detect insulin resistance early, before clinical disease appears. We do not recommend routine screening of patients using fasting insulin measurements because of the following liabilities: The problems with assay procedures, the inability of the measurement to accurately indicate the presence of insulin resistance, the lack of a well-defined cut point differentiating normal from abnormal, and the lack of data establishing whether modification of insulin resistance has an impact on outcomes available.[4]

The present study shows that IR can be detected in up to 40.6% and 37.5% sensitivity by criteria laid down by ATP III compared with McA index and fasting insulin levels respectively. Moreover it had high specificity rates when compared to above indirect indices. Validity of criteria laid down by ATP when compared to McA and FI in the case of determination IR was not satisfactory.

In studying the diagnostic sensitivity and specificity, we further found that the sensitivity is low, although specificity is high. More than 50% of the patients would not be detected as having IR by criteria laid down by ATP. Therefore we suggest that these clinical and biochemical markers have to be adopted for high sensitivity to determine IR rather than more expensive indirect indices.

CONCLUSION

Criteria laid down by ATP III to diagnose IRS had a sensitivity 40.6% and 37.5%; specificity of 80% and 70% when compared with McA and fasting insulin indices respectively. Further, there was no satisfactory agreement between criteria laid down by ACE and indirect indices to diagnose IRS. Therefore, this study leads us to formulate more sensitive and specific clinical criteria for detection of IRS among patients with type 2 DM.

REFERENCES

1. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. Endocr Pract 2005;11:126-34.
2. Hirschler V, Ruiz A, Romero T, Dalamon R, Molinari C. Comparison of different anthropometric indices for identifying insulin resistance in school children. Diabetes Technol Ther 2009;11:615-21.
3. Reaven GM. Pathophysiology of insulin resistance in human disease. Physiol Rev 1995;75:473-86.
4. Mishal AA. Acanthosis Nigricans: A new analysis of associated endocrine and malignant disorders. Ann Saudi Med 1997;17:651-3.
5. Patrice DC, Jacques A, Miguel AI, Marjorie P, Claude K, Bastelica D, *et al.* Metabolic Endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56:1161-72.
6. Granberry MC. Fonseca VA. Insulin resistance syndrome: Options for treatment. South Med J 1999;92:2-14.
7. Tilg H, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. Mol Med 2008;14:222-31.
8. DeFronzo RA, Ferrannini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-94.
9. Ferrannini E, Mari A. How to measure insulin sensitivity. J Hypertens 1998;16:895-6.
10. Howard G, Bergman R, Wagenknecht LE, Haffner SM, Savage PJ, Saad MF, *et al*. Ability of alternative indices of insulin sensitivity to predict cardiovascular risk: Comparison with the "minimal model." Ann Epidemiol 1998;8:358-69.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Teacher DF, Tumer RC. Homeostasis model assessment: Insulin resistance and beta cell function from fasting plasma glucose and insulin concentration in man. Diabetologia 1985;28:412-9.
12. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care 2003;26:3320-5.
13. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, *et al.* Quantitative insulin sensitivity check index: A simple, accurate method of assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402-10.
14. McAuley KA, Williams SM, Mann JI, Walker RJ, Ledwis-Barned NJ, Temple LA, *et al.* Diagnosing insulin resistance in the general population. Diabetes Care 2001;24:460-4.
15. Foong MM, Awang B. The modified NCEP ATP III criteria may be better than the IDF criteria in diagnosing Metabolic Syndrome among Malays in Kuala Lumpur. BMC Public Health 2010;10:678. Available from: http://

www.biomedcentral.com/1471-2458/10/678.
16. Robert OB. Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation 2002;106:3140-1.
17. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, *et al*. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683-9.
18. Stevan ES, Ken W, Eleuterio F, Ralph AF, Clifton B, Stern MP. Identification of individuals with insulin resistance using routine clinical measurements. Diabetes care 2005;54;2:333-9.
19. Semple RK, Cochran EK, Soos MA, Burling KA, Savage DB, Gorden P, *et al*. Plasma adiponectin as a marker of insulin receptor dysfunction: Clinical utility in severe insulin resistance. Diabetes Care 2008;31:977-9.

How to cite this article: Hettihewa LM, Weerarathna TP. Comparison of McAuley/fasting insulin indices with ATP III clinical criteria for the diagnosis of insulin resistance in type 2 diabetes mellitus. J Pharmacol Pharmacother 2011;2:165-9.
Source of Support: Nil, **Conflict of Interest:** None declared.