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Review

Insulin Resistance Syndrome; the challenges of diagnosis

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Insulin resistance syndrome (IRS) is a clinical condition that has continued to dominate clinical research and discourse in the past two decades. This stems from its associated role in a number of disease conditions which include cardiovascular disease, diabetes mellitus, polycystic ovary disease, steatohepatitis, obstructive sleep apnoea and some cancers. While there is consensus among many authorities on many of the clinical outcomes of IRS, though still evolving on a regular basis, there remains on-going debate as regards the diagnostic pre-requisites. This arises primarily because it is a cluster of risk factors and these factors are adjudged for propensity to cause disease based on certain levels or measurement cut-points. Unfortunately these cut-off levels of the risk factors are affected by other variables like race, sex, age and sometimes biases arising from outcomes of studies which are usually slanted towards a given clinical outcome, oftentimes cardiovascular disease or diabetes mellitus. Overtime five organizations have presented the most applied set of diagnostic criteria utilized in clinical practice and these include the National Cholesterol Education Program, World Health Organization, American Association of Clinical Endocrinologists, International Diabetic Federation and European Group for the study of Insulin Resistance. Although these set of criteria basically have common determinant parameters such as obesity, atherogenic dyslipidaemia, hypertension, insulin resistance, pro-inflammatory and prothrombotic states, they differ in the weightiness allotted to some parameters vis a vis IRS diagnosis. This review appraises these diagnostic criteria and highlights the inherent challenges in such multiplicity especially in our environment which *ab initio*, contributed little or nothing to the generation of the diagnostic cut-offs of the parameters.

Keywords: Insulin resistance, dyslipidaemia, cardiovascular, atherogenic, obesity, prothrombotic, hypertension

INTRODUCTION

The explosion of research and educational material on the insulin resistance syndrome (IRS) attests to the recognition of its importance by clinicians. (ACE, 2003), IRS variously called metabolic syndrome, syndrome X, cardiometabolic syndrome etc, has been implicated in a lot of clinical outcomes which include cardiovascular disease (CVD), diabetes mellitus(DM), polycystic ovary disease(PCOD) (Julie, 2003), cholelithiasis (Grundy 2004a), obstructive sleep apnoea (OSA) (Coughlin et al., 2004), non-alcoholic steatohepatitis (NASH) (Grundy et al., 2004b), asthma (Grundy et al., 2004b) and cancers of the breast, ovary and colon (Labib, 2003). In the future the list of the clinical outcomes is expected to increase (ACE-position statement, 2003).

However, despite the recognition of the importance of this syndrome, identifying individuals who have the IRS is difficult as there is no simple clinically available test to diagnose it (Sobngwi et al., 2001; ACE, 2003). In the absence of a straightforward diagnostic test or definitive clinical trials, identification and treatment of a syndrome as complex as this, require thoughtful evaluation of the best available evidence and consensus among researchers and clinicians (ACE, 2003). From the foregoing, it is obvious why there are multiple diagnostic criteria for this clinical condition. Initially, four organizations had recommended clinical criteria for the diagnosis of IRS namely the National Cholesterol Education Program (NCEP) (NCEP-Expert Panel, 2000; Stern and Williams, 2004), the World Health Organisation (WHO)(WHO, 1999; NCEP- Expert Panel, 2001), the American Association of Clinical Endocrinologists (AACE) (ACE, 2003), and the European Group for the study of

Insulin Resistance (EGIR) (IDF 2005). Their criteria are similar in many aspects, but they also reveal fundamental differences in positioning of the predominant causes of the syndrome (Grundy et al, 2004).

Not too long ago, a fifth clinical criteria, seeking to harmonize other existing criteria for worldwide use in clinical practice was introduced by the International Diabetes Federation (IDF) (IDF 2005). It is of note however that the NCEP and WHO criteria are the two definitions which have wide acceptance, and form the basis of most research on metabolic syndrome thus far.

However one major drawback from this multiplicity of diagnostic criteria is the variation of prevalence of IRS depending on the criteria (Cavali et al., 2010; Tran et al., 2011).

Each of these criteria for the definition of IRS will be reviewed briefly.

NCEP'S ATP – III Criteria

According to ATP III which prefers the term metabolic syndrome to insulin resistance syndrome, a diagnosis of IRS, can be established if three (3) out of a total of five (5) risk factors are present. These risk factors and their diagnostic cut offs are as outlined in Appendix I. The primary clinical outcome of IRS as identified by the above criteria, suggests coronary heart disease (CHD) or cardiovascular disease (CVD) more strongly than type 2 diabetes mellitus. This has been buttressed by studies like the West of Scotland Coronary Prevention Study (WOSCOPS), which highlights the focus of ATP III on CHD risk (Gloria, 2002; Sattar and Gaw, 2003). Infact, some studies have pointed out ATP III as being only modestly successful at identifying insulin resistance and consequently predicting diabetes mellitus risk (Karen et al., 2004).

The risk factors which form the basis of ATP III selection criteria are generally those widely accepted as components of IRS. These include obesity, hypertension, hypertriglyceridaemia, low HDL and impaired glucose regulation. Under this criterion each of the five (5) individual risk factors has equal or equivalent diagnostic weight (Hanson et al., 2002). The obesity component, unlike in the AACE or part of the WHO criteria is as assessed by waist circumference. This is due to the fact that visceral obesity of which the former is a index of, is a better predictor of metabolic and cardiovascular complications (Abate and Garg, 1995; Fujimoton, 1995; Nieves et al., 2003).

Explicit demonstration of insulin resistance is not required for diagnosis; however, most persons meeting ATP III criteria will be insulin resistant (Grundy et al., 2004b). Finally, the presence of type 2 diabetes does not exclude a diagnosis of IRS.

In a bid to evaluate the suitability of NCEP-ATP III criteria some authorities have introduced modifications in their studies which have lead to improved agreement with the WHO criteria (Rosenbaum et al., 2005).

WHO Criteria

In 1998, a WHO consultation group outlined a provisional classification of diabetes that included a working definition of the IRS, culminating in a final report being released in 1999 (WHO, 1999). The guideline group also recognized cardiovascular disease as the primary outcome of the syndrome. However, it viewed insulin resistance as a required component for diagnosis (WHO, 1999). In this criteria, insulin resistance was defined as one of the following: type 2 diabetes, impaired fasting glucose (IFG); impaired glucose tolerance (IGT), or for those with normal fasting glucose (<110mg/dl) a glucose uptake below the lowest quartile for background population under hyperinsulinaemic, euglycaemic conditions.

Under this criteria, insulin resistance, in addition to two (2) other risk factors out of five (5) are required for the diagnosis of IRS (Appendix II). Unlike in the ATP III criteria, microalbuminuria is a criterion. Higher blood pressure cut-off points are required than in the ATP III, and body mass index (or increased waist: hip ratio) is used instead of waist circumference. Similar to the ATP III criteria, the presence of diabetes mellitus does not exclude the diagnosis of metabolic syndrome. It is of note that the requirement of objective evidence of insulin resistance in those with normal glucose tolerance gives more predictive power for diabetes mellitus than does ATP III. (Grundy et al., 2004b; Hanley et al., 2003). The WHO criteria has higher diagnostic cut-off points than the ATP III criteria on characteristics like high density lipoprotein (HDL) cholesterol and hypertension.

Insulin resistance being a sine qua non for the diagnosis of IRS in the definition has affected the ease of application of WHO criteria. This is basically because specific measurements of insulin resistance are not clinically practical (Sattar and Gwa, 2003). Plasma insulin concentrations are often used as surrogate measures of insulin resistance, but their ability to predict insulin resistance is relatively modest .(Karen et al., 2004). Additionally, because techniques for measuring plasma insulin concentrations are not standardized, values will show considerable variations from one clinical laboratory to another (Karen et al, 2004)[31]. This is further worsened by the fact that no specific plasma insulin concentration has been validated as a predictor of CVD (Karen et al., 2004; Palanippan, 2004).

It is true that evidence clearly shows insulin resistance as a fundamental defect linking individual components of metabolic syndrome, the strength of association of insulin resistance to these components is variable in different populations and even within populations (DeFronzo and Ferrannini, 1991).

In addition the use of body mass index (BMI) instead of waist circumference(WC) may be viewed by some as a demerit given that studies have shown WC or other indices of abdominal obesity as more sensitive predictors of obesity complications than BMI (Nieves et al., 2003).

In view of the aforementioned reasons, coupled with the fact that it requires neither an oral glucose tolerance test nor measurement of microalbuminuria, ATP III criteria is more frequently used than the WHO criteria (Stern, 2004). In a bid to improve the ease of application of the WHO criteria, some studies have undertaken some modifications of the definition. For example, a modified WHO defining criteria was used for the Kuopio Finish study[38] whereby insulin resistance was defined by hyperinsulineamia (upper quartile of population) or fasting plasma glucose $\geq$110mg/dl; additionally microalbuminuria was removed as a criterion. Such modifications will enable the WHO criteria to be readily applied in routine clinical practice and large clinical trials.

AACE Criteria

The American Association of Clinical Endocrinologists (AACE) has a set of clinical criteria which is however loose and non-specific. These criteria which appear to be a hybrid of those of ATP III and WHO, however does not have a defined number of risk factors specified and diagnosis is left to clinical judgement (Grundy et al., 2004). These criteria (Appendix III), assume greater significance as the number of risk factors increase pointing to greater magnitude of abnormalities (ACE-position statement, 2003). Under these criteria, patients whose degrees of hyperglycaemia fulfil the diagnostic criteria for type 2 diabetes mellitus are excluded, unlike in the ATP III and WHO criteria. As such the AACE views IRS not as a clinically specific disease state, but as a group of abnormalities that tend to cluster together with increased predisposition to type 2 DM and/or CVD (ACE-position statement, 2003). In view of the focus of AACE criteria to provide a sensitive screen to identify individuals at increased risk to have insulin resistance, 2-hour post-glucose challenge is listed separate from fasting glucose as a marker of impaired glucose regulation. Additionally 2-hour post glucose challenge is taken as a superior determinant of the risk of insulin resistance syndrome and development of CVD than fasting plasma glucose concentration (Abate and Garg, 1995; DECODE-Study group, 2001). In fact in patients without impaired fasting glucose (IFG), 2hour post glucose challenge is recommended, when an abnormality is clinically suspected(Grundy et al., 2004b)[22.]. Under AACE, BMI is preferred to waist circumference as an index of obesity and viewed as a physiological variable that increases insulin resistance rather than a criterion for diagnosis of the insulin resistance syndrome (ACE-position statement, 2003).

The AACE makes it clear that the criteria as outlined in Appendix III is not to be used as rigid recipe for classification of individuals as being insulin resistant or sensitive (ACE-position statement, 2003). Consequently, prudence is advised in the form of lifestyle and/or pharmacological interventions, in individuals whose values exceed even if only one of the cut-points, outlined therein. This portrays the aforementioned looseness of the criteria which may be the reason why it has not had much acceptance by many.

EGIR Criteria

The European Group for the study of Insulin resistance (EGIR) in 1999 fashioned out a set of guidelines for the diagnosis of IRS. Like the AACE group, they prefer the term insulin resistance syndrome instead of metabolic syndrome but differ from the former in having a specific numbers of risk factors to diagnose the condition. The EGIR criteria are similar to the WHO criteria in that insulin resistance or hyperinsulinaemia is a sine qua non for diagnosis in non-diabetic subjects (Baulka and Charles, 1999; British Nutrition Foundation report, 2004). Due to the priority given to insulin resistance, the EGIR criteria is bedeviled by the same factors working against the WHO criteria because it has been noted that insulin resistance is not synonymous with metabolic syndrome (Gloria, 2002; ACE-position statement 2003).

However while in the WHO criteria, impaired fasting glucose is listed as an index of insulin resistance, the EGIR makes it a separate entity. Also in contrast to the WHO, the EGIR excludes microalbuminuria as a criterion and utilizes only waist circumference to define obesity (Appendix IV).

The EGIR criteria also use higher cut-off values for hypertriglyceridaemia and low HDL-cholesterol than the WHO criteria.

IDF Criteria

The International Diabetes Federation (IDF) definition of IRS is the latest of all the criteria proposed for use in clinical practice. The IDF definition recognizes central obesity and insulin resistance as important causative factors of the syndrome. Central obesity, easily assessed using waist circumference, is a pre-requisite risk factor for the diagnosis, whereas insulin resistance which is difficult to measure in day-to-day clinical practice is not an essential requirement (International Diabetes Federation, 2005). As such under this criteria, an individual must have central obesity as defined by waist circumference, and other two (2) additional risk factors out of four (4), to be diagnosed as having IRS (Appendix V). One distinguishing aspect of the IDF criteria is that the pre-requisite criterion (central obesity) is both gender

and ethnic-group specific. As such there are different cut-points for Europoids, South Asians, Chinese, Japanese etc, and these are not judged based on country of residence or domicile (International Diabetes Federation, 2005) (Appendix VI). This approach by IDF was probably prompted by some studies such as the study on Asians using the NCEP ATP III criteria which highlighted the need for different cut points for males and females from South Asia and Japan (Azziz et al., 2003; Tan et al., 2004).

Unfortunately the IDF criteria use European central obesity cut-points for sub-Saharan Africans as there are no specific data for the latter presently (appendix VI). In a bid to increase the effectiveness of the IDF criteria for IRS diagnosis, the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) tried to reconcile the pre-requisite criterion of central obesity with IDF but ended up recommending higher cut points for males and females respectively (Alberti et al, 2009) This further brings to the fore the need for more research works in our environment as regards this clinical condition.

CONCLUSION

Whereas the status of the clinical entity IRS as a risk factor for a horde of disorders is not in doubt, there is a lack of consensus amongst authorities concerning the diagnostic benchmark for its assessment in individuals, which also mirrors its various nomenclature.

This is basically due to variability of the cluster of risk factors which make up of the syndrome. Most of these factors which are assessed based on morbidity and/or mortality outcomes have been shown to be race- or ethno-subjective.

In addition biases towards certain given clinical outcomes of IRS by clinicians cum researchers have contributed to the differences in the diagnostic parameters.

In our environment, it is imperative that population based studies are done to garner reference values and medical cut-off or decision limits for some of these parameters such that suitable applicable criteria relevant to the population here are adapted.

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Appendix I

ATP III Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
* Abdomen obesity given as waist circumstance	
- Men	>102 cm
- Women	>88cm
*Triglyceride	≥150mg/dl
*HDL Cholesterol	
- Men	<40 mg/dl
- Women	< 50 mg/dl
*Blood pressure	≥ 130/≥ 85mmHg
*Fasting Plasma Glucose	≥ 110 mg/dl

Any **3** of the **5** risk factors defines metabolic syndrome in an individual.

Appendix II

WHO clinical criteria for metabolic syndrome

Insulin resistance, identified by **1** of the following

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- Or for those with normal fasting glucose levels (<110mg/dl) glucose uptake below the lowest quartile for background population under investigation, under hyperinsulinaemic euglycaemic conditions.

Plus any **2** of the following:

- Anti-hypertension medication and/or high blood pressure (≥140mmHg systolic or ≥ 90 mmHg diastolic)
- Plasma triglycerides ≥150mg/dl
- HDL Cholesterol <35mg/dl in men or <39mg/dl in women
- BMI > 30kg/m^2 and/ or waist hip ratio > 0.9 in men, > 0.85 in women.
- Urinary albumin excretion rate > 20µg/min or albumin: creatinine ratio > 30mg/g.

Appendix III

AACE Clinical Criteria for diagnosis of Metabolic Syndrome

Risks factor Components	Outpoint for abnormalities
Overwieght / Obesity	BMI > 25kg/M^2
Elevated triglycerides	> 150 mg/dl
Low HDL Cholesterol	
Men	< 40 mg/dl
Women	<50mg/dl
Elevated blood pressure	> 130/85mmHg
2 Hours post-glucose challenge	> 140mg/dl
Fasting glucose	110 126mg/dl
Other risk factors	Family history of type 2 diabetes hypertension or CVD. Polycystic ovary syndrome. Sedentary lifestyle, advancing age ethnic groups having high risk for having high risk for type 2 diabetes or CVSD

Appendix IV

EGIR CRITERIA FOR METABOLIC SYNDROME

* Insulin resistance or hyperinsulinaemia (Non diabetic subjects only), and any **2** of:

1. Fasting Plasma glucose > 110mg/dl
2. Dyslipidaemia
   - Triglycerides >177mg/dl
     and/or
   - HDL Cholesterol <35mg/dl
     and/or
   - Treated for dyslipidaemia
3. Hypertension
   - Blood pressure > 140/90 mmHg
   - Medication for hypertension
4. Central Obesity
   - Waist Circumference > 94cm (Males
     > 80 cm (Female)

Appendix V

International Diabetes Federation (IDF) Criteria for metabolic syndrome

* Central Obesity (defined as waist circumference > 94cm for Europid men and > 80cm for Europid women, with ethnicity specific values for other groups).

* Plus any two (**2**) of the following four (**4**) factors:-

- Raised TG level. > 150mg/l or specific treatment for this lipid abnormality.
- Reduced HDL Cholesterol, < 40mg/dl in males and < 50mg/dl in females, or specific treatment for this
- lipid abnormality.
- Raised blood pressure: systolic BP > 130 or diastolic BP >85mmHg, or treatment of previously
- diagnosed hypertension.
- Raised fasting plasma glucose (FFG) > 100mg/dl, or previously diagnosed type 2 diabetes.

Appendix VI

Ethnic specific values for waist circumference for IDF Criteria for metabolic syndrome.

Country/ethnic Group		**Waist Circumstance**
Europids	Male	≥ 94 cm
In the USA, the ATP III Values (102 cm males 88cm female) are likely to continue to be used for clinical purposes.	Female	≥ 80cm
South Asians Based on a Chinese, Malley and Asian – Indian Population	Male	≥ 90 cm
	Female	≥ 80cm
Chinese	Male	≥ 90 cm
	Female	≥ 80cm
Japanese	Male	≥ 85 cm
	Female	≥ 90cm
Ethnic south and central American	Use south until more available	Asian recommendation specific data are
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab Populations)	Use European data until more specific data are available.	