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Measurement of Insulin Resistance (IR) - HOMA index model

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ABSTRACT

Insulin resistance (IR) is one of the major pathogenetic mechanism causing diseases of glucose metabolism like type 2 diabetes mellitus (T2DM). IR syndrome is one of the important public health issues. Effective approaches with certain benefits and drawbacks have been sought for easy screening. One of them is the Homeostasis Model Assessment of IR (HOMA-IR) which is used to assess β-cell function and IR. For people of different races, age groups, sexes, and who have varied health issues and comorbidities, there are distinct HOMA-IR cut-off points. Due to the lack of precise criteria, only few countries recommend cut-off values for their populations, which limits its usage in routine clinical practice.

Improvement in its use may help to prevent T2DM in high-risk populations. This research project reviews the recent research papers on IR and HOMA-IR.

KEYWORDS:

Insulin Resistance (IR), Homeostasis Model Assessment of IR (HOMA-IR), type 2 diabetes mellitus (T2DM).

INTRODUCTION:

Insulin Resistance (IR) is associated with a decrease in the sensitivity of muscle and adipose tissue to insulin, a reduction in the ability to produce glucose, and an increase in fat production in the liver.[1] IR is a condition in which insulin produces worse biological response than usual. There are numerous ways to evaluate IR at the moment, with the homeostatic model assessment being the most used (HOMA-IR). [2]

In 1960, Yalow and Berson, with the introduction of radioimmunoassay, stated that "Insulin resistance is a common increase in the dose of insulin to maintain a normal response." In 1923, Kylin combined hypertension, hyperglycaemia, and gout into a syndrome and over time, this syndrome changed to being called metabolic syndrome, IR syndrome, or polymetabolic syndrome. In 1988, Gerald Reaven named the syndrome X and considered it a background factor in CV disease.[3]

In 1998, the World Health Organization (WHO) gave a unified definition as "Considered insulin resistance when the HOMA index is greater than the highest quartile in the control group". [3,4,5,6,7]

This research project explains IR and its relation with DM as well as HOMA-IR while also mentioning its different cut-off values.

Pathogenesis of insulin resistance (IR)

IR pathogenesis is broadly divided into two types: genetic or acquired IR [4,5,8]:

i. Genetic IR where there is an alteration in insulin receptors, signal changes after combination, altered β3-Adrenergic receptors. It includes genetic or primary target cell defects, auto antibodies to insulin, and accelerated insulin degradation. Mitochondrial dysfunction may also play an important role in the development of IR and associated complications.

ii. Acquired IR is when there is an increase in the levels of anti-regulation, drug- induced hormones, glucose intoxication, glutamine enzyme, glucose transporter defect (GLUT-4), lipid toxicity (cytokines and hormones from fat cells), decrease in insulin secretion rate, and hormone activity in tissue. Acquired IR is usually a result of obesity, inactivity, aging, and certain medical conditions or medications that counteract insulin activity. Also, secondary IR is observed in hyperthyroidism, Cushing's syndrome, acromegaly, trauma, burns, and stress. The role of infection and inflammation is currently of interest because the inflammatory mechanism can impair insulin activity and may explain the IR that can occur in non-obese individuals. [2,8,9,10]

Homeostasis model assessment of IR index (HOMA-IR index)

HOMA-IR index is calculated by the formula

HOMA-IR = [glucose (Go) (mmol/L) ×insulin (Io) (μU/L)]/22.5

Go: plasma glucose during fasting, Io: plasma insulin during fasting. [2,7]

Normal level of HOMA-IR is <2.5.

HOMA or log (HOMA) is extensively used in large epidemiological studies, prospective clinical trials, and research.[2]

In research settings where assessing insulin sensitivity/resistance is of secondary interest or when feasibility issues preclude the use of direct measurement by hyperinsulinemia euglycemic clamp (HIEC), it may be appropriate to use log (HOMA). Correlation coefficient of HOMA-IR with HIEC under different conditions are: Normal glucose tolerance (0.65; $p < .0001$), impaired glucose tolerance (0.56, $p < .0001$) and with type 2 diabetes mellitus (0.51, $p < .0001$) [2,8,11-15]

Since IR is a widely generic topic, there are many different definitions that exist for it. HOMA-IR is typically employed because it has excellent reliability in determining IR, despite the fact that there are other ways to assess IR. The main benefit of the HOMA model is that a patient must only have their blood collected once when fasting. As a result, it can be used in both clinical settings and large-scale epidemiological investigations because it does not require a high level of technical competence and costs substantially less per participant than the HIEC. It does not, however, offer details regarding the insulin and stimulated glucose systems.

HOMA-IR may not provide accurate results in patients whose beta cell function is substantially compromised or non-existent.[2]

Hyperinsulinemia euglycemic clamp (HIEC)

The technique of "insulin clamp" was first introduced by De Fronzo in 1979 and till date, remains the "gold standard" to assess IR. After an overnight fast, 5 -120 mU/m2/min insulin is infused intravenously at a constant rate (hyper insulinemic) and the blood glucose level is monitored at 5-10 minutes interval, while 20% dextrose is given IV at a variable rate in order to "clamp" blood glucose concentration in the normal range (euglycemic). After several hours of constant insulin infusion, steady-state conditions can be achieved for plasma insulin, blood glucose, and the glucose infusion rate. [2,11] The glucose infusion rate for the last 30 minutes of the test, known as "steady state," will determine IR. This is an intrusive technique and quite complex than HOMA-IR. The main limitations of the HIEC are that it is time-consuming, labour-intensive, expensive, and requires an experienced operator to manage the technical difficulties. Moreover, the clamp utilizes steady-state insulin levels that may be supraphysiological. This results in a reversal of the normal portal to the peripheral insulin gradient. Thus, the glucose clamp may not accurately reflect insulin action and glucose dynamics under physiological conditions that a dynamic test, such as an oral meal or oral glucose load may determine.[11,13,15]

Insulin Resistance (IR) and Diabetes mellitus (DM)

Definition

The concept of IR was proposed as early as 1936 and is generally defined as reduced biological action of insulin, such as inhibition of hepatic glucose production and insulin- mediated glucose disposal.[16,17]

IR increases the incidence of metabolic syndrome (MS), which has emerged as a major pathophysiological factor in the development and progression of many common non-communicable diseases, including T2DM, polycystic ovary disease, dyslipidaemia, hypertension, cardiovascular disease and obesity. [18-20]

Inducement of IR

Diet

Obesity and IR frequently coexist, which may be because dietary fat has long been linked to IR. [21] Recent research has suggested that the intake of simple sugars, and particularly fructose, is also a factor that contributes to IR. [22]

Another possibility is that systematic overeating, which is a common cause of both IR and obesity. Systematic overeating has the potential to cause IR and obesity due to the frequent administration of excess glucose and fructose, which increase triglyceride levels in the blood, stimulate insulin secretion, and fats, which may be easily absorbed by adipose cells and result in the formation of fatty tissue in a hypercaloric diet. [21]DM

Recent research and experimentation have uncovered a non-obesity related connection betwee n IR and T2DM. [23] Increased insulin sensitivity or remission of T2DM has long been noted in patients who have undergone some form of bariatric surgery. [24]

Increased insulin sensitivity or remission of T2DM has also been noted in diabetic or insulin-resistant non- obese rats that have had their duodenum surgically removed. [25]

Hepatitis C virus (HCV)

HCV also makes people three to four times more likely to develop IR and T2DM. In addition, people infected with the HCV who develop DM probably have susceptible insulin- producing cells and probably would have developed DM anyway, but much later in life. The extra IR caused by HCV apparently brings on DM at age 35 or 40, instead of 65 or 70. [21,26] Sedentary lifestyle

A sedentary lifestyle increases the likelihood of developing IR. [27] For each 500 kcal/week increment in energy expenditure as a result of physical activity, the lifetime risk of T2DM decreases by 6%. [28] According to one study, vigorous exercise at least once a week reduced the risk of T2DM in women by 33%. [29]

Pathogenesis of DM

Reaven proposed a model for DM caused by IR whereby IR manifests in susceptible individuals in the early stages of DM, and particularly in T2DM. [21] Resistance to insulin stimulated glucose uptake is evident in most patients with impaired glucose tolerance (IGT) or non-insulin dependent DM (NIDDM) and in 0-25% of non-obese individuals with normal oral glucose tolerance. [30,31]

The pathogenesis of DM is as follows:

i. When food containing carbohydrates is consumed, the digestive system breaks carbohydrates down into sugar that then enters the blood. As blood sugar levels rise, the hormone insulin is secreted by the islets of Langerhans in the pancreas to prompt cells to absorb sugar for energy or storage.
ii. Adverse environmental factors or disease can cause cells to fail to respond to the normal actions of insulin, resulting in IR.
iii. Once IR develops and the body produces insulin, the body's cells fail to respond to insulin and are unable to use it effectively (Impaired Glucose Tolerance; IGT).
iv. When the condition develops further, apoptosis of islet cells occurs and glucose metabolism is disrupted, leading to clinical DM. [32]

Calculation of IR and its use in the primary prevention of T2DM:

Calculation of IR

The Homeostasis Model Assessment of IR (HOMA-IR) has proved to be a robust tool for the assessment of IR and is the index of IR that is most widely used in large population studies. [33-35] The HOMA of β-cell function and IR was 19first described in 1985. [36,37]

HOMA-IR and HOMA-%β are determined using the following simplified equations:
HOMA-IR = (FPI × FPG) / 22.5;
HOMA-%β = (20 × FPI) / (FPG - 3.5)381
Here, FPI is the fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose (mmol/L). [38]
Use of HOMA-IR in the primary prevention of T2DM
Primary T2DM prevention entails preventing T2DM from arising or identifying high-risk populations and adopting precautions to lessen T2DM. [21]

Generally, categories of increased risk for DM (pre-DM) in guidelines on DM are:

i. FPG of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (Impaired Fasting Glucose; IFG)
ii. 2-h plasma glucose in the 75-g oral glucose tolerance test (OGTT) of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (Impaired Glucose Tolerance; IGT)
iii. an A1C of 5.7-6.4%. [39]

Testing of asymptomatic people to detect T2DM and assess the future risk of DM should be considered for adults of any age who are overweight or obese (BMI≥25 kg/m2) and who have one or more additional risk factors for DM according to the following indexes:

i. physical inactivity
ii. a first-degree relative with DM
iii. high-risk race/ethnicity
iv. women who delivered a baby weighing 9 lb or who were diagnosed with gestational DM
v. hypertension
vi. an HDL cholesterol level of 35 mg/dL (0.90 mmol/L) and/or a triglyceride level of 250 mg/dL (2.82 mmol/L)
vii. women with polycystic ovary syndrome (PCOS)
viii. A1C ≥ 5.7%, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) on previous testing
ix. other clinical conditions associated with IR (e.g., severe obesity)
x. a history of cardiovascular disease (CVD).

Location and time	Sample size	Population characteristics	Threshold value	Criteria	References
Sweden, 2000	n = 4,816	Healthy population	2.0	75th percentile	[44]
France, 2002	n = 1,153	Age: 35 - 64; Healthy population	3.8	75th percentile	[45]
Caucasus, 2006	n = 1,156	Rural population; non-diabetic	2.29	75th percentile	[46]
Brazil, 2006	n = 1,317	Age: 40 ± 12 years; BMI: 34 ± 10 kg/m2	2.77	90th percentile	[47]
U.S., 2008	n = 2,804	Age ≥ 20; normal BMI and fasting glucose	2.73	66th percentile	[48]
Iran, 2010	n = 3,071	Adult individuals; ages: 25-64 years	3.875	ROC curve	[49]
Iran, 2011	n = 1,036	Women of reproductive age	2.63	95th percentile	[50]
Japan, 2012	n = 6,868	Non-diabetic subjects	1.7	ROC	[51]
China, 2013	n = 3,203	Ages: 6-18 years (children and adolescents)	3.0	95th percentile	[52]
Portugal, 2014	n = 1,784	Non-diabetic individuals in a Cardiology ward; BMI < 25 Kg/m2; FPG < 100 mg/dL	2.33	90th percentile	[53]

Table 1. Main cut-off values of HOMA-IR in recent literature (sample size ≥ 1000)

At age 45, testing of asymptomatic individuals without these risk factors should start. [21] Although the major role of IR is cited in point ix. above, guidelines for diagnosis of DM have not defined the cut-off values of IR for high-risk groups. [40]

Principles for determination of HOMA-IR cut-off values

The use of predetermined HOMA-IR cut-off values to identify individuals with IR leads to certain issues. The determination of HOMA-IR cut-off values affects the identification of IR and healthcare management for individuals of different genders, ages, or races and individuals with different diseases and complications. [41,42]

Although IR is usually defined as a value greater than the 75th percentile value for non- diabetic subjects according to the World Health Organization (WHO) [43], the cut-off values reported in the literature vary widely (Table 1). [44-53]

CONCLUSION:

The HOMA (Homeostatic Model Assessment) index is a widely used method for measuring insulin resistance (IR) in both clinical and research settings. The HOMA index uses fasting glucose and insulin levels to estimate IR, providing a simple, non-invasive and cost- effective method for assessing the body's insulin sensitivity.

One of the advantages of the HOMA index is its ease of use, as it requires only two fasting measurements - fasting glucose and insulin levels - which can be obtained from a standard blood test. The HOMA index has been shown to be highly correlated with other more complex and invasive methods of measuring IR, such as the hyperinsulinemia euglycemic clamp (HIEC).

In terms of limitations, the HOMA index is based on a mathematical model, and like all models, its accuracy can be affected by various factors, including the presence of conditions such as obesity, type 2 diabetes, and liver disease. Additionally, the HOMA index only provides a snapshot of insulin sensitivity at a single point in time, and may not reflect dynamic changes in insulin sensitivity over time. Also, there is a need for proper cut-offs based on the type of population.

Overall, the HOMA index is a useful tool for measuring insulin resistance, providing valuable information for the diagnosis, monitoring and management of insulin resistance and associated conditions such as type 2 diabetes. However, it should not be used as the sole method for assessing insulin resistance, and should be interpreted in conjunction with other clinical and laboratory findings.

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