JMSCR Vol||04||Issue||09||Page 12705-12710||September 2016

www.jmscr.igmpublication.org
Impact Factor 5.244
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: http://dx.doi.org/10.18535/jmscr/v4i9.65

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in the Diagnosis of Insulin Resistance and Prediabetes

Authors
Dr Deepak Bhosle[1], Dr Asif Sayyed[2], Dr Abhijeet Bhagat[3], Dr Huzaif Sheikh[4], Dr Vasundhara Londhe[5]
[1]Professor and Head, [2,5]Chief Residents, [3]Assistant Professor, [4]Senior Resident,
Dept of Pharmacology, M.G.M Medical College Aurangabad (MS)-India
Corresponding Author
Dr Asif Sayyed
Chief Resident, Dept of Pharmacology, M.G.M Medical College Aurangabad (MS)-India

Abstract
Type 2 diabetes mellitus consists of metabolic disturbances characterised mainly characterized by hyperglycemia which usually result from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. In clinical practice its very difficult to establish how much part of this metabolic disturbances is due to lack of insulin and how much it is due to peripheral resistance to insulin. In many of the cases of type 2 diabetes mellitus metabolic syndrome is present for many years before development of full blown type 2 diabetes mellitus. Metabolic syndrome is a cluster of biochemical and physiological abnormalities associated with the development of cardiovascular disease and type 2 diabetes. Insulin resistance is one of the important determinants of development of metabolic syndrome and then type 2 diabetes mellitus. Insulin resistance is increasing in many parts of the world due to sedentary lifestyle, substance abuse, obesity and harmful food habits. Several methods including estimation of blood glucose and insulin levels during fasting or after oral or intravenous glucose overload, have been used. But due to the simplicity of its determination and calculation, insulin resistance assessment by the homeostatic assay (HOMA-IR) is becoming more popular technique in clinical practice as well as in various epidemiological studies. Unlike type 1 diabetes, type 2 diabetes mellitus is gradual in onset and its diagnosis is usually delayed for many years. Early treatment of hyperglycaemia, hyperlipidemia and other metabolic irregularities reduces the cardiovascular risk in these patients. But these benefits are usually denied to patients mainly due to delay in diagnosis. In fact many of the patients admitted with myocardial infarction are diagnosed with type 2 diabetes while in intensive care units for myocardial infarction. Unlike in type I diabetes mellitus where insulin is deficient consequent to immune mediated destruction of B cells in type 2 diabetes there is Insulin resistance. Insulin resistance in pre diabetic stages can be diagnosed by using various methods. Some simple methods, from which indices can be derived, have been validated. These indices are used depending upon whether they are to be used for epidemiological or clinical purposes. For clinical purposes Quantitative insulin sensitivity check index (QUICKI) and homeostasis model assessment- insulin resistance (HOMA-IR) are most commonly used while for epidemiological purposes indices like Belfiore, Cederholm and Stumvoll index are suitable. This review explains the utility of homeostasis model assessment- insulin resistance (HOMA-IR) for the diagnosis of insulin resistance which is hallmark of pre diabetic state. The purpose of this paper was to review the current information available about HOMA-IR and its use in pre diabetes.

Keywords: *Homeostasis model assessment- Insulin resistance (HOMA-IR), Prediabetes, Insulin resistance, Metabolic syndrome.*

Introduction

The metabolic syndrome refers to the co-occurrence of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia and hypertension. These conditions are interrelated and share underlying mediators, mechanisms and pathways[1]. It is well known fact that an individual risk of developing cardiovascular disease is dependent upon many factors which may be modifiable or non modifiable. The modifiable risk factors include exercise, weight reduction, control of blood pressure and blood sugar levels, cessation of smoking and other substance abuse[2]. While some of the risk factors like advanced age, male gender, family history of premature heart disease and certain genetic disorders causing cardiovascular diseases like homocystinuria are non-modifiable risk factors[3]. The metabolic syndrome is one of modifiable causes of cardiovascular disease. According to guidelines from the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions. (1) Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia) (2)Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension) (3)Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia) (4) HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C) (5) Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women [4].

Various methods are recommended for decreasing or delaying the detrimental effects of insulin resistance on body. These includes Lifestyle change and weight loss followed by diet modification [5]. Drug treatment such as statins for elevated LDL, Niacin for decreased HDL, Fibrates and omega 3 fatty acids for elevated triglyceride levels and metformin for insulin resistance. But for all this it is essential that the insulin resistance and pre diabetic state should be diagnosed at an early stage. The test which was considered to be gold standard for measurement of insulin sensitivity was Hyperinsulinemic euglycemic clamp (HEC) but it is time consuming and expensive [(5)]. It is for this reason that various simplified indices are developed and studied in last 2 decades. These indices determine insulin resistance by using the data from oral glucose tolerance test. Other indices are calculated by calculated by using fasting plasma concentrations of glucose, insulin and triglycerides. HOMA-IR is a simple test to diagnose insulin resistance in pre diabetic stages. It is derived from the product of the insulin and glucose values divided by a constant, that is, calculated by using the following formula: fasting glucose (mg/dL) X fasting insulin (μU/mL) / 405 (for SI units: fasting glucose (mmol/L) X fasting insulin (μU/L) / 22.5). A value greater than 2 indicates insulin resistance. There is a small difference in cutoff values of HOMA-IR in various studies. Some studies have suggested the normal cutoff value to be 1.85 and also suggested that The threshold levels must be modified by age in non-diabetic population[(6)].

Example-1

A 40-year-old male, weighing 70 kg, with a height of 170 cm, and thus a BMI of 24.2 kg/m2. He is non-diabetic, non-hypertensive and has a normal lipid profile. He have a family history of diabetes mellitus in father. There is no family history of hypertension, cardiovascular disease or stroke. His fasting blood sugar is 90 mg/dl, and fasting insulin level of 4.2 μU/ml.

HOMA-IR = Insulin (μU/ml) X Glucose (mg/dl)/405

By above equation HOMA-IR value comes to 0.93. This values is normal and the person can be told that he doesn't have any e/o insulin resistance.

Example-2

A 42-year-old female, weighing 80 kg, with a height of 168 cm, and thus a BMI of 28.3 kg/m2. She is non-diabetic, non-hypertensive and has a normal lipid profile. She have a family history of diabetes mellitus in both her parents. There is no family history of hypertension or stroke. One of her relatives suddenly died due to massive myocardial infarction. Now she is worried about

getting diabetes. Her fasting blood sugar is 120 mg/dl, and fasting insulin level of 8.9 µU/ml.

HOMA-IR = Insulin (µU/ml) X Glucose (mg/dl)/ 405

By above equation HOMA-IR value comes to 2.64. She is definitely developing insulin resistance. She should be informed about this and lifestyle and dietary modification should be advised.

Table 1: Estimation of HOMA-IR and its inference.

Glucose (mg/dl)	Insulin (µU/ml)	HOMA-IR Value	Inference
90	4.2	0.93	No insulin resistance
120	8.9	2.64	Insulin resistance

The utility of HOMA-IR in assessment of Insulin resistance has been validated even in pediatric age group and adolescents. HOMA-IR is a simple and non-expensive method for evaluation of insulin sensitivity. It has a good correlation with the results of glucose clamp test in subjects with mild diabetes without significant hyperglycemia. The limitation of HOMA-IR is that it is difficult to be used in patients who have received insulin for any reason. Moreover its use is also controversial in patients with poor glycemic control and in those patient who have severe β cell dysfunction [(7)].

Insulin resistance due to any cause like metabolic syndrome, hypertension, hyperlipidemia, coronary artery disease, hepatic dysfunction the polycystic ovary syndrome may manifest as increased HOMA-IR values [(8)].

Discussion

In 1976, Robert Turner and Rury Holman developed the concept that fasting plasma insulin and glucose levels were determined, in part, by a hepatic-beta cell feedback loop. They further showed that both plasma insulin levels and blood glucose levels were impaired and postulated that in diabetes insulin control of hepatic glucose efflux acts as insulin 'sensor'.This according to them causes the basal plasma glucose to rise until the reduced number of beta cells are sufficiently stimulated to secrete normal basal insulin levels. They suggested that glucose regulation was of secondary importance to maintenance of basal insulin secretion. According to the authors the degree of basal hyper glycaemia provides a bioassay of the decrease in insulin secretion capacity, enabling one to estimate the number of functioning beta cells. The observed insulin secretion in diabetes was thought to be similar to that predicted from this estimate [(9)]. Later in 1987 Matthews Dr et al proposed that steady-state basal plasma glucose and insulin concentrations are determined by their interaction in a feedback loop. A computer-solved model was used to predict the homeostatic concentrations which arise from varying degrees beta-cell deficiency and insulin resistance. Comparison of a patient's fasting values with the model's predictions was done which allowed a quantitative assessment of the contributions of insulin resistance and deficient beta-cell function to the fasting hyperglycaemia (homeostasis model assessment, HOMA). The accuracy and precision of the estimate was determined by comparison with independent measures of insulin resistance and beta-cell function using hyperglycaemic and euglycaemic clamps and an intravenous glucose tolerance test [(10)].

HOMA analysis allows assessment of inherent β-cell function and insulin resistance and can characterize the path physiological basis in those with impaired glucose tolerance. Longitudinal data in normal subjects who go on to develop abnormal glucose tolerance is particularly informative. The use of HOMA to make comparisons across ethnic groups is valid. One of the important considerations while calculating HOMA-IR is that insulin secretion is pulsatile that means the use of the mean of three samples or more taken at 5-min intervals to compute HOMA is theoretically better than a single sample[(11)]. Other important considerations while calculating HOMA-IR is that it should not be solely relied upon in patients who have already been on insulin treatment, poor glycemic control and near total dysfunction of b cells. Some studies have also

suggested that HOMA-IR values are increased in non-alcoholic fatty liver disease[12]. Hence in these patients also raised HOMA-IR values should be cautiously interpreted. Homa-IR is also validated to be used in children and adolescents. Kurtoğlu S et al conducted a study to determine HOMA-IR cut-off levels in the prepubertal and pubertal periods. They concluded that though HOMA-IR can be used in children and adolescents cut-off values which depend on gender and pubertal status, should be used in evaluation of insulin resistance[13]. Another interesting aspect of HOMA-IR is that its values are increased in vitamin-D deficiency. It is a well known fact that vitamin-D is the most important regulator of calcium metabolism in body. In addition to calcium metabolism other roles of vitamin D are believed to involve immunoregulatory function by activating innate and adaptive immunity and cytokine release, and other molecular actions to maintain glucose homeostasis and mediate insulin sensitivity by a low calcium status, obesity, or by elevating serum levels of parathyroid hormone. These effects of vitamin D deficiency, either acting in concert or alone, all serve to increase insulin resistance and consequently cause increase in HOMA-IR values[14]. It must be remembered that HOMA-IR is an independent predictor of cardiovascular disorders in type 2 diabetes. Study conducted by bonora et al used fatal and nonfatal coronary, cerebrovascular, and peripheral vascular disease as well as ischemic electrocardiographic abnormalities and vascular lesions identified by echo-Doppler to assess the cardiovascular disease and concluded that the improvement of insulin resistance might have beneficial effects not only on glucose control but also on cardiovascular diseases in patients with type 2 diabetes [15]. While the diagnosis of insulin resistance and pre diabetes states cannot be overemphasized the limitations of HOMA-IR test should always be kept in mind. Like already emphasised this test is of not much significance in patients who had already been on insulin treatment, those with total destruction of B cells and those with impaired glucose tolerance test. Some of the other studies have suggested that HOMA-IR test may have significant limitation in predicting insulin resistance and beta-cell dysfunction in older people. Chang A.M et al compared sensitivity to insulin (S(I)) and acute insulin response to glucose (AIRg) from FSIGT with HOMA models and concluded that there was a weak Agreement between HOMA beta-cell and AIR[16]. Another important factor while determining or studying HOMA-IR in patients is the different cutoff values in different population. Cutoff values of HOMA-IR changes depending upon demography, gender, presence of vitamin D deficiency and other co-morbid conditions like hepatic diseases and polycystic ovarian syndrome (PCOS) etc. There are some studies which have suggested that the use cutoff values of HOMA-IR based upon the cardio metabolic risk rather than percentile of population distribution to define insulin resistance would increase its clinical utility in identifying those patients in whom the presence of multiple metabolic risk factors imparts an increased metabolic and cardiovascular risk [17]. There is wide variations in the cutoff levels of HOMA-IR some studies have determined it to be 2-2.5 in Indian population. This inference was based upon the fact that HOMA-IR less than 2.5 appeared to be associated with no apparent coronary artery disease or other cardiovascular complications [18]. The cutoff value is different for different population like one large study study comprising of Hispanic population of 1854 adults concluded that cutoff value of HOMA-IR was 3.80. This value was far greater than popular clinical cutoff value of 2.6 [19]. If various limitations of HOMA-IR values and factors affecting its cut-off values in different population is kept in mind then it's one of the most reliable, less invasive, inexpensive, and less labor-intensive method to measure insulin resistance[20].

Conclusions

1) Homeostasis model assessment of insulin resistance is one of the most reliable, less invasive, inexpensive, and less labor-intensive method to measure insulin resistance in patients with prediabetes.

2) The cutoff values of HOMA-IR is not universal and dependent upon demography, gender, presence of vitamin D deficiency and other co-morbid conditions like hepatic diseases and polycystic ovarian syndrome (PCOS) etc.
3) HOMA-IR is not reliable in the settings of patients who had already been on insulin treatment, those with total destruction of B cells and those with impaired glucose tolerance test.
4) HOMA-IR is an independent predictor of cardiovascular disease in type 2 diabetes mellitus and decrease in HOMA-IR might have beneficial effects not only on glucose control but also on cardiovascular diseases in patients with type 2 diabetes.
5) HOMA-IR value of less than 2.5 was found to be associated with no adverse outcome in patients who had diabetes since more than 10 years.

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