Review

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Optimal cut-off values for the homeostasis model assessment of insulin resistance (HOMA-IR) and pre-diabetes screening: Developments in research and prospects for the future

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Summary **Diabetes mellitus (DM) appears to be increasing rapidly, threatening to reduce life expectancy for humans around the globe. The International Diabetes Federation (IDF) has estimated that there will be 642 million people living with the disease by 2040 and half as many again who will be not diagnosed. This means that pre-DM screening is a critical issue. Insulin resistance (IR) has emerged as a major pathophysiological factor in the development and progression of DM since it is evident in susceptible individuals at the early stages of DM, and particularly type 2 DM (T2DM). Therefore, assessment of IR *via* the homeostasis model assessment of IR (HOMA-IR) is a key index for the primary prevention of DM and is thus found in guidelines for screening of high-risk groups. However, the cut-off values of HOMA-IR differ for different races, ages, genders, diseases, complications, *etc*. due to the complexity of IR. This hampers the determination of specific cut-off values of HOMA-IR in different places and in different situations. China has not published an official index to gauge IR for primary prevention of T2DM in the diabetic and non-diabetic population except for children and adolescents ages 6-12 years. Hence, this article summarizes developments in research on IR, HOMA-IR, and pre-DM screening in order to provide a reference for optimal cut-off values of HOMA-IR for the diagnosis of DM in the Chinese population.**

Keywords: Insulin resistance; homeostasis model assessment of insulin resistance (HOMA-IR); diabetes mellitus type 2

1. Introduction

Diabetes mellitus (DM) has become prevalent with changes in lifestyle, threatening to reduce life expectancy for humans around the globe (*1,2*). Globally, there were a total of 382 million patients with DM in 2013 (*3*). The projections for the future constitute a dramatic call to countries and their governments. The International Diabetes Federation (IDF) has estimated that there will be 642 million people living with the disease by 2040 and half as many again who will be living with undiagnosed DM, unknowingly at risk from its disabling, life-threatening complications (*4*). This means that pre-DM screening is a critical issue.

In addition, DM appears to be increasing rapidly in China. The overall prevalence of DM was estimated to be 11.6% in the Chinese adult population in 2010, which is considerably higher than its prevalence of less than 1% in 1980 (*5*). Recent studies in China have found that there were 92.4 million persons with DM and 148.2 million persons with pre-DM in 2013, and 60% of patients were not diagnosed (*6*).

Type 2 DM (T2DM) is a complex, polygenetic hereditary disease associated with both heritable and environmental factors. Insulin resistance (IR) is a major pathophysiological factor in the development and progression of DM, and IR is also evident in a variety

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of metabolic diseases, such as obesity, hypertension, and dyslipidemia (*7-10*). Epidemiological studies have shown that about 25% of the population has IR and that the prevalence of IR is more than 80% in patients with T2DM (*11-13*). Guidelines for primary prevention of T2DM should identify categories of increased risk for DM (pre-DM), but many do not include the cut-off values of IR (*14,15*).

IR is now used as a screening index for the primary prevention of DM. This article examines developments in research on IR. Determining optimal HOMA-IR cut-off values would facilitate the diagnosis of DM in the Chinese population.

2. IR and DM

2.1. *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, dyslipidemia, hypertension, cardiovascular disease and obesity (*18-20*).

2.2. *Inducement of IR*

2.2.1. *Diet*

IR commonly coexists with obesity, which may because dietary fat has long been implicated as a driver of IR. Recent research has suggested that the intake of simple sugars, and particularly fructose, is also a factor that contributes to IR (*21*). Another possible explanation is that both IR and obesity often have the same cause, systematic overeating. Systematic overeating has the potential to lead to IR and obesity due to repeated administration of excess levels of glucose, which stimulate insulin secretion; excess levels of fructose, which raise triglyceride levels in the bloodstream; and fats, which may be readily absorbed by adipose cells and up as fatty tissue in a hypercaloric diet.

2.2.2. *DM*

Recent research and experimentation have uncovered a non-obesity related connection between IR and T2DM (*22*). Increased insulin sensitivity or remission of T2DM has long been noted in patients who have undergone some form of bariatric surgery (*23*). 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 (*24*).

2.2.3. *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 (*25*).

2.2.4. *Sedentary lifestyle*

A sedentary lifestyle increases the likelihood of developing IR (*26*). For each 500 kcal/week increment in energy expenditure as a result of physical activity, the lifetime risk of T2DM decreases by 6% (*27*). According to one study, vigorous exercise at least once a week reduced the risk of T2DM in women by 33% (*28*).

2.3. *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. 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 (*29,30*).

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 (IGT); *iv*) When the condition develops further, apoptosis of islet cells occurs and glucose metabolism is disrupted, leading to clinical DM (*31*).

3. Calculation of IR and its use in the primary prevention of T2DM

3.1. *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 (*32-34*). The HOMA of β-cell function and IR was first described in 1985 (*35,36*). 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)

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

Location and time	Sample size	Population characteristics	Threshold value	Criteria	References
Sweden, 2000	*n* = 4,816	Healthy population	2.0	75th percentile	(*43*)
France, 2002	*n* = 1,153	Age: 35 - 64; Healthy population	3.8	75th percentile	(*44*)
Caucasus, 2006	*n* = 1,156	Rural population; non-diabetic	2.29	75th percentile	(*45*)
Brazil, 2006	*n* = 1,317	Age: 40 ± 12 years; BMI: 34 ± 10 kg/m^2	2.77	90th percentile	(*46*)
U.S., 2008	*n* = 2,804	Age ≥ 20; normal BMI and fasting glucose	2.73	66th percentile	(*47*)
Iran, 2010	*n* = 3,071	Adult individuals; ages: 25-64 years	3.875	ROC curve	(*48*)
Iran, 2011	*n* = 1,036	Women of reproductive age	2.63	95th percentile	(*49*)
Japan, 2012	*n* = 6,868	Non-diabetic subjects	1.7	ROC	(*50*)
China, 2013	*n* = 3,203	Ages: 6-18 years (children and adolescents)	3.0	95th percentile	(*51*)
Portugal, 2014	*n* = 1,784	Non-diabetic individuals in a Cardiology ward; BMI < 25 Kg/m^2; FPG < 100 mg/dL	2.33	90th percentile	(*52*)

Here, FPI is the fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose (mmol/L) (*37*).

3.2. *Use of HOMA-IR in the primary prevention of T2DM*

Primary prevention of T2DM means preventing T2DM from developing or identifying high-risk groups and taking steps to mitigate T2DM. 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) (IFG); or *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) (IGT); or *iii*) an A1C of 5.7-6.4% (*38*).

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/m^2) 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). Testing of asymptomatic people who lack these risk factors should begin at age 45.

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 (*39*).

3.3. *Principles for determination of HOMA-IR cutoff 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 (*40,41*).

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) (*42*), the cut-off values reported in the literature vary widely (Table 1) (*43-52*).

4. Prospects for the future

As this review has elaborated, IR develops in susceptible individuals in the early stages of DM, and particularly T2DM. IR can be measured using HOMA-IR. At the present time, however, the glucose clamp technique is used to quantify beta-cell sensitivity to glucose and insulin (*53*). The glucose clamp technique offers a highly reproducible method of assessing sensitivity to glucose and tissue sensitivity to insulin, but it is complex and difficult to use. Thus, HOMA-IR tends to be a more convenient and efficient way to measure IR even though it is calculated solely from the FPI and PFG.

Using HOMA-IR to diagnose DM is an unscientific approach because DM can be caused by IR as well as excess insulin. That said, IR is clearly associated with

a pre-diabetic state. The cut-off values of HOMA-IR differ for different races, ages, genders, diseases, complications, *etc*. (*54*). An individual with a high HOMA-IR should nevertheless seek medical advice, exercise, and change his or her lifestyle, regardless of whether or not the individual has a metabolic disease. The cut-off values of HOMA-IR need to be examined in non-diabetic subjects in order to devise a standard for the primary prevention of DM.

At the present time, China has not published an official index to gauge IR for primary prevention of T2DM in the diabetic and non-diabetic population except for children and adolescents ages 6-12 years. The current review should provide a reference for the control of T2DM (*55*).

The current study has several limitations. First and foremost, a specific HOMA-IR cut-off value has not been calculated based on gender, age, race, *etc*., and only reference values are indicated. Second, variations in cut-off values of HOMA-IR in different countries have not been analyzed.

5. Conclusion

In conclusion, this article has defined DM, it has explained how DM can be induced, and it has described the role of IR in the pathogenesis of DM. This article has also summarized developments in research on IR and it has emphasized the significance of primary prevention of T2DM. Different HOMA-IR values for different races, ages, genders, diseases, complications, *etc*. are described for use in primary prevention of DM. This article should provide a reference for optimal cut-off values of HOMA-IR for the diagnosis of DM in the Chinese population.

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