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# ++*Diagnostic Usefulness of HOMA-β and HOMA-IR in Diabetes Mellitus – A Review*

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## ABSTRACT

*Homeostatic model of assessment (HOMA) is a statistical method for assessing pancreatic β – cell function (HOMA - β) and insulin resistance (HOMA – IR). Both are calculated using fasting plasma glucose (FPG) and insulin but with different formulae. A modified form of HOMA is emerging using Connective Peptide (C - Peptide) concentration, but studies based on this have been very limited. More than 500 research papers have been published about the use of HOMA to assess Diabetes Mellitus (DM) and Cardiovascular Disease (CVD), but the main area of its application is in the field of DM. HOMA – IR has been diagnostically more useful in all types of DM and obesity, in assessing prediabetes and detecting DM in the elderly. It has also been found to be useful during the gestational period. HOMA indices have been widely used along with Glycosylated Hemoglobin (HbA1c), but good standardization is very important for better clinical use of HOMA. This review article has given condensed highlights on the clinical usefulness of HOMA in monitoring the control of DM at various stages using simple formulae to calculate HOMA indices. The parameters used were FPG and insulin. HOMA indices were also compared with other parameters such as HbA1c and two emerging parameters Obstatin and Visfatin, but very few studies have been reported about their clinical usefulness. The contents of this review articles can be very useful for future researchers to expand the application of HOMA indices to the other diseases induced by the uncontrolled DM.*

**Key words:** *HOMA –IR, HOMA – β, Diabetes Mellitus, FPG, Insulin, HbA1c, T2DM*

## INTRODUCTION

Diabetes mellitus is an important metabolic disorder with several micro and macro vascular complications [1]. Technologies have progressed during the last 50 years towards finding novel DM monitoring markers. Several markers such as Continuous Glucose monitoring (CGM), HbA1c, Glycated albumin (GA) and Fructosamine (FA) have been used as markers to monitor DM control. Each marker has its merits and demerits. The routinely used tests to screen DM have been Fasting Plasma Glucose (FPG), Post Prandial Plasma glucose (PPPG) and HbA1c. Of late, some calculated markers using measured parameters were being used to understand the status of DM. The main focus of this review article was to discuss the diagnostic usefulness of HOMA indices, HOMA-IR and HOMA- β which have been calculated using FPG and Insulin.

**HOMA and Diabetes Mellitus**

Homeostasis Model of Assessment (HOMA) has been used to assess β -Cell function (Homa-β) of pancreases as well as Insulin Resistance (HOMA-IR). The above two diabetes status assessment models could be calculated using FPG and Insulin. Extensive research studies have been done in the past on the use of HOMA- β and HOMA-IR for understanding β -cell function as well as IR in a variety of diseases induced by DM. The first model of HOMA was reported in 1985. Although computer models have been available to calculate them, calculations using measured parameters to get approximate values are now extensively used in monitoring DM status. The reliability of the use of these models depends upon the accuracy of Glucose and Insulin results [2].

Studies have confirmed that IR is a major risk factor for the onset of Type 2 Diabetes Mellitus (T2DM) in individuals without DM or obesity. The highest HOMA-IR was associated with HbA1c and FPG after adjusting for the other HOMA-IR variables. The normal value for HOMA-IR is < 2.6 and in a study, women had lower values compared to men. HbA1c and FPG showed significant correlation to HOMA – IR for both sexes. Increased HOMA-IR values were inversely associated with 1,5 Anhydroglucitol (1,5 AG) compared with normal, but only for men. IR may influence glycemic control even in lean and non – DM Asian population [3].

The optimal cut off value for HOMA-IR for identifying dysglycemia and T2DM was reported as 1.37, and cut off values of 1.4 and 2.0 were observed in subjects with persistent normal glucose tolerant (NGT) in Chinese population, and it could be used as reference in clinical research related to the assessment of IR [4]. The onset and development of T2DM were accelerated by IR, and exercise was recommended to improve the IR. In a study, it was found that swimming improved the oral glucose tolerance test (OGTT) and IR. It also improved the FPG, baseline insulin, HbA1c, Triglycerides (TGs) and Total Cholesterol (TC) and also increased the high density lipoprotein cholesterol (HDL-c). Therefore, swimming has been recommended to improve glycemic control and insulin sensitivity in T2DM patients [5].

Although, many studies have been done on the clinical usefulness of HOMA-IR, the lack of standardization prevails. The best cut off value for HOMA-IR to identify IR was 3.8. In Hispanic population, 39.1% of the individuals have been identified as having HOMA-IR > 3.8. These observations were based on the routinely used cut off value of 2.6. In order to improve public health based on HOMA-IR, the cut off value of 3.8 was used in Hispanic population [6]. Measurements of HOMA –IR would be helpful in detecting early complications associated with T2DM and selecting the best treatment options. In a study, the median HOMA-IR was found to be useful in detecting early complications associated with T2DM, and selecting the best treatment options. The median HOMA-IR score was 2.91 for patients and 1.97 for controls ($p < 0.0001$). In a studied group of DM patients, the complications observed were 26% retinopathy, 26% neuropathy; and HOMA-IR scores were higher in patients with T2DM compared to the controls, and higher scores were observed with increased risk for retinopathy, neuropathy, nephropathy, coronary artery disease (CAD) and peripheral vascular diseases [7]. The quantitative insulin sensitivity check index (QUICKI) in patients without metformin therapy showed a significant correlation to FPG and C-Peptide and a significant correlation between HOMA-IR and QUICKI in all studied groups, but no significant correlations were observed between FPG and C-Peptide index with the other clinical parameters. The above observations strongly suggested that significant correlations existed between HOMA-IR and QUICK I indices in T2DM patients [8].

HOMA-IR has also been linked to visceral adipose tissue (VAT) and Hypomagnesaemia. Such individuals suffered from metabolic syndrome (MS) and T2DM. Patients with HOMA-IR < 2.8 were found to be younger with lower BMI and less VAT. Hypomagnesaemia was found to be more prevalent among T2DM patients than in obese without T2DM. Serum magnesium (Mg) showed negative correlation to HOMA-IR, but logistic regression study did not show any association. Hence, serum Mg may not be a determinant to assess IR in obese and T2DM patients [9].

A study has predicted that MS and its components showed sex differences for T2DM and dysglycemia patients. The cut off value of HOMA-IR to identify dysglycemia was 1.6 for both sexes. The cut off value for T2DM was 2.87 for men and 2.6 for women. The accuracy of identifying T2DM patients gradually decreased with increasing age in both sexes. IR is the main risk factor for both T2DM and dysglycemia. To detect early T2DM in elderly, it has been important to check IR index, insulin secretory function as well as MS components [10].

Obestatin has been emerging as a new marker to assess obese patients with T2DM. It has shown significant and negative correlations to BMI, basal Insulin and HOMA-IR in DM patients. Hence, Obestatin may contribute to

BMI regulation, and Insulin sensitivity could be affected by circulating Obestatin levels [11]. In a study done on Iranian population, it was found that triglyceride index may be a useful parameter to assess IR instead of HOMO-IR. However the authors have suggested more studies to be done based on the large sample size using gold standard laboratory tests to assess the specificity and sensitivity of this marker [12].

IR was found to be a better tool compared to Insulin secretion to assess T2DM. However, when both parameters were entered into the same regression model, both significantly predicted T2DM. HOMA-IR could be used as a single prediction to assess cell function in epidemiological studies for mass screening of population to identify T2DM [13].

Univariate regression analysis has shown a significant correlation between log transformed HOMA-IR and clamp IR before and after the treatment of T2DM patients. Both slopes and intercepts in the regression equation did not show any significant correlations. Hence, HOMA-IR may be a useful parameter for diagnosing IR and for follow-up during the treatment of T2DM [14].

Maternal age, pre-pregnancy, BMI and family history of DM were some of the factors that might lead to Gestational Diabetes Mellitus (GDM) in pregnant women. Both Insulin and HOMA-IR values using venous blood of umbilical cord showed significantly higher values compared to the control groups. The umbilical HOMA-IR values showed positive correlation to maternal HOMA-IR and fasting insulin. Further, HOMA-IR was found to be significantly higher in late pregnant GDM women compared to the controls [15]. Lifestyle intervention in GDM had shown improvements in metabolic measures of insulin, glucose and HOMA-IR compared to the controls. Such lifestyle interventions had shown improvements even after 1 – 2 years of delivery by such women, suggesting that lifestyle education might show improvements in pregnancy outcome in women with GDM [16].

In a study, low Omestin-1 levels were found to be present in Impaired Glucose Regulation (IGR) in T2DM patients than Normal Glucose Tolerance (NGT). Further, serum Omestin-1 level was found to be negatively correlated to BMI, HOMA-IR, fasting insulin and Tumor necrosis Factor-α (TNF-α), IL-β and PG. Hence, the lack of Omestin-1 may contribute to the development of IR [17]. HOMA indices have been extensively used in epidemiological studies to assess the diabetic risk. The level of fasting insulin, FPG and HOMA-IR were found to be significantly higher in DM than the controls. The association between HOMA-IR and HOMA-β to diabetic risk remained significant in all ethnic groups of Whites, Blacks, Hispanic and Asians. HOMA-IR was found to be a stronger predictor compared to the other markers. In a multi ethnic cohort study, high HOMA-IR and HOMA-β were independently associated with an increased risk to DM [18].

In a study, Leptin, HOMA-IR and HOMA-β were found to be increased in a group screened for pre-pregnancy of patients with GDM. No significant correlation was found between HOMA-IR and adipokines. HOMA-IR showed positive correlation to HOMA-β and negative correlation to HOMA-S (insulin sensitivity). Both Leptin and HOMA-IR were increased in pregnant GDM patients with obesity. Also, both were positively correlated with BMI before pregnancy and at screening for GDM [19]. The association between FPG and HbA1c with the incident DM was found to be non-linear, and at higher FPG values, the association became stronger in 2 hours and fasting insulin also showed association to incident DM. Future studies should be undertaken to assess for non-linear association between glycemic and incident T2DM [20].

Prediabetes was more common in women with parental T2DM (PT2DM) and previous GDM (PGDM). PGDM was more prevalent than PT2DM, and in this group increased TC, fibrinogen and lower HOMA-β were observed compared to PT2DM. Post challenge GTT correlated independently with high sensitive C - reactive protein (hs-CRP), FPG and HOMA-IR. Cardio metabolic risk factors were also prevalent in this group. FPG was found to be an important cardio metabolic risk factor associated with HOMA-IR [21].

Both Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) defined pre-diabetic, and they were directly related to HOMA-IR. The elevated risk for developing T2DM could be ascertained by IFG and IGT tests. Under this condition, it was important to assess ß-cell function in order to decide on the therapeutic interventions which could delay the progression of IFG/IGT to frank diabetes [22]. In a study, there were 29% of individuals in the IFG-110 compared to 5% of IFG-100 and 0.3% of Normal Fasting Glucose (NFG). In each of the above group, those having higher initial level of glucose progressed to DM, and base level HOMA-β was not lower but higher in individuals who developed DM in NFG group. All these observations were found to be in conflict with the previous observations that HOMA-β predicted the development of DM [23].

T2DM subjects with MS had more HOME-IR than the controls even when insulin secretion was less and comparable to the controls. Both HOMA-IR and HOMA-S were related to the number of metabolic abnormalities. While HOMA-IR was positively associated with BMI, Waist to Hip ratio (WHR), FPG, body fat, HOMA-S was negatively associated with WHR, FPG and TC, but positively with metabolic rate. In multiple regression analysis, the percent of body fat was shown as an independent predictor of HOMA-IR and WHR of HOMA-S. Subjects with MS had increased IR, and decreased insulin secretion compared to the controls. Life style modifications have shown an improvement in IR and insulin secretion, and controlled the various components of MS [24].

Hyperglycemia is the main determinant for the development of various chronic diabetic complications [25]. There was a correlation between deficient β -cell function assessed by HOMA model to hyperglycemia clamps as well as to IGT test. The precisions obtained for HOMA-IR and HOMA-β which were 31% and 32%, respectively might limit its use for the correlation studies. Hence, basal glucose and insulin interactions must be carefully interpreted by better HOMA results [26]. The intensive intervention has shown improvement in β -cell function as assessed by HOMA-β which showed an acute insulin response. The acute insulin response has shown improvement in insulin treated group, but not in oral hypoglycemic therapy group. Hence, early intensive insulin therapy must be initiated in newly diagnosed T2DM for better outcome on recovery and maintenance of β -cell function [27].

DM subjects with HbA1c values > 6.5 – 7 % showed an increase in HOMA-β index. However, HOMA-β showed a significant decrease at HbA1c>7.0, and progressive decline as HbA1c values increased from 7.0% to 8-9%. At a HbA1c level of 7.9%, a 62% reduction in ß cell function was observed independently of age, gender, BMI, Blood Pressure (BP), lipid levels and hepatic enzymes. However, IR showed a significant increase with increased HbA1c values. Elevated HbA1c values were proportional to the reduction in β -cell function [28].

The new parameter, Standard Deviation of Blood Glucose (SDBG) and HbA1c were significantly correlated to HOMA-β. After the adjustments of multiple cofounders, both HbA1c and SDBG were associated with HOMA-β. In patients with newly diagnosed T2DM, both HbA1c and glycemic variability were associated with HOMA-β cell functions. Studies with large number of patients would be required to prove these observations [29]. Both median HOMA-IR and HOMA-β scores were higher in over weight adolescents than lean adolescents and adolescents with T2DM. The mean glucose in adolescents with T2DM was 1.8 fold higher than that of overweight adolescents, although, the median C-Peptide with T2DM was lower than that of overweight adolescents, but the differences was not statistically significant. Among Peruvian adolescents with T2DM, IR was found to be more prominent compared to β -cells dysfunction [30]. HOMA-β and Disposition Index (DI) were lower in GDM than NGT post-partum women. HOMA-β did not show a significant difference between GDM pregnant and women after delivery with the history of GDM. Hence, pregnant women with GDM had a pancreatic cell defect that might remain after birth. Hence, these women were prone to develop T2DM after delivery [31].

Pregnant women with NGT did not reveal significant IR compared with the controls, but HOMA-β was found to be higher. This might be due to the excess β cell function to maintain glucose homeostasis. However, the subset of pregnant women with GDM had significantly higher HOMA-IR and HOMA-β values compared to the pregnant women with NGT. The pregnant GDM women might show severe IR even without the previous history of dyslipidemia. HOMA-IR was found to be an independent predictor of total outcome even in women with NGT. HOMA-β showed a strong independent prediction of total outcome in all the pregnant women with GDM [32].

The HOMA-IR values in overweight women with NGT and in women with GDM were significantly higher than those with normal weight women with NGT. It was also found that HOMA-IR in women with GDM increased significantly during pregnancy, but its values in normal and overweight women with NGT did not change with the advancement of gestation. QUICKI values in overweight women with NGT as well as in women with GDM were significantly lower than those with normal weight women. Insulin sensitivity in women with GDM declined with the advance of pregnancy [33].

A study has shown that BMI was associated with HOMA-IR, HOMA-β insulin index as well as to the lower level of Insulin Sensitivity Index Composite (ISI comp) and DI. Using multi regression model, it has been proved that BMI showed independence and positive associations with HOMA-IR, HOMA-β and ISI clamp, but was inversely correlated to DI. These observations have been noted in Korean patients with T2DM [34]. HOMA

and Continuous Glucose Insulin Model Assessment (CGIMA) using immunoreactive insulin have been recommended for the better assessment of β cell function which could distinguish across the subjects with NGT, IGT and T2DM for assessing first phase insulin response [35].

Area under Curve of Insulin (AUCINS) and HOMA-β in hyperinsulinemia group were higher compared to the normal group. 12 week exercise did not show any significant change in BP, BMI, PG, lipids between hyperinsulinemia and control. However, there was a significant decrease in AUCINS, HOMA-ß and HOMA-IR. Hence, exercise might prevent pre-diabetic IR and ß cell dysfunction in non-diabetic young off springs of diabetic parents [36]. High FPG and BMI might show impairment in ß-cell function when assessed using calculated HOMA-ß. In male subjects, the marked deficiency of ß-cell function might be due to the impaired Insulin sensitivity to obesity and physical inactivity [37].

The young newly diagnosed T2DM with the increased TGs had the worst lipid and glucose profiles with the high insulin levels. The ß-cell function as assessed by HOMA-ß and modified β -Cell function Index (MBCI) might initially increase along with TGs, but might decrease with further increase in TGs. A Chinese study has found that hyper Triglyceridemia influences the clinical characteristics of ß-cell function in newly diagnosed T2DM patients. Hence, better management of TGs might reduce lipo-toxicity and improve glucose homeostasis in newly diagnosed T2DM [38]. HOMA-IR was found to be significantly increased in Addison's disease (AD) group compared with Cognitively Normal (CN) adults. Higher HOMA-IR in CN adults was associated with poor verbal episodic memory, executive function and global cognition. Hence, IR might contribute to the reduced cognitive performance compared to the normal adults [39].

The prevalence of IR was high in obese children and adolescents. No predictive cut point values for IR or ISI for IGT and FPG, insulin levels or HOMA-IR and HOMA-β were found to be effective as screening tools. OGTT might be required in all subjects with high risk. More studies would be required to identify the metabolic precursors leading to the development of T2DM [40]. In early pregnancy, GDM women would gain more weight compared to the non-GDM women with normal weight. GDM was mainly associated with IR in all the obese pregnant women. Plasma Visfatin, adiponectin, resistin and progesterone levels were higher in GDM than non-GDM women. Low Visfatin and adiponectin and high progesterone levels due to high saturated fat intake by GDM pregnant women might lead to large gestational age babies. Studies have suggested the importance of evaluating daily energy intake during pregnancy according to pre-pregnancy BMI [41].

The strong independent predictors of T2DM were overweight, central fat distribution, dyslipidemia, HT and poor glycometabolic control. Reduced insulin sensitivity could be found even when T2DM patients were isolated and well controlled [42]. In T2DM patients, while HOMA-IR Estradiol (E2), E2/Testosterone (E2/T) significantly increased, Bone Mineral Density (BMD), ISI, Sex Hormone Binding Globulin (SHBG) was decreased compared to the controls. Serum T levels of T2DM and Diabetic Osteoporosis (DO) group showed a negative correlation compared to HOMA-IR, and positively correlated to fasting Insulin and ISI. Hence, reduced T in T2DM with DO might promote IR [43]. In a clinical trial, it was found that overweight and obese children with HOMA-IR at $75^{th}$ percentile were significantly associated with MS. It is therefore important to establish percentile for HOMA-IR to understand MS among T2DM. Adding BMI along with HOMA-IR would certainly help in understanding MS better [44].

## CONCLUSION

Many studies have recommended HOMA indices as the alternate tools to assess the implications arising out of DM. Many studies have predicted its clinical usefulness in a variety of diseases, but mostly in DM. This review articles have highlighted the following outcomes:

- HOMA-IR has been a good statistical tool to assess prediabetes, its control and prognosis.
- The parameters, FPG and Insulin used to calculate both HOMA –IR and HOMA – β- must be measured with the state of the art methodology.
- Measurements of HOMA –IR would be helpful in detecting early complications associated with T2DM and selecting the best treatment options.
- IR is the main risk factor for both T2DM and dysglycemia.
- HOMA-IR could be used as a single prediction to assess cell function in epidemiological studies for mass screening of population to identify T2DM.
- FPG was found to be an important cardio metabolic risk factor associated with HOMA-IR.

- Both HOMA-IR and HOMA-S were related to the number of metabolic abnormalities.
- Life style modifications have shown improvements in IR, insulin secretion and controlling the various components of MS.
- HOMA –IR usefulness in GDM is an emerging area which needs further standardization.
- Along with HOMA- β, Insulin sensitivity index should also be measured for better correlation.
- HOMA indices were also found to be useful in CVD.
- Omestatin and Visfatin have been the two emerging markers to substantiate the usefulness of HOMA indices, but very few studies have been reported about its clinical usefulness.
- All DM profile tests were found to be associated with HOMA indices.
- More studies would be required to establish standardized protocol for the use of HOMA indices.

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