

Study of Insulin Resistance in Type 2 Diabetes Mellitus by Homa-IR Score

Purohit A¹, Tiwari V²

¹Dr Ashish Purohit, Assistant professor, Department of Medicine, LN Medical college, Bhopal, ²Dr Varsha Tiwari, Senior resident, Department of pediatrics, LN Medical college, Bhopal, MP, India

Address for Correspondence: Dr. Varsha Tiwari, Email: dr.varshatiwari021@gmail.com

Abstract

Introduction: Insulin resistance precedes and strongly predicts the development of type 2 diabetes mellitus, estimation of insulin resistance was helpful in detection of early complications and selecting the treatment options, hence the present study was planned. HOMA estimated insulin resistance is an independent predictor of cardiovascular disease in type-2 diabetic subjects **Materials and Methods:** A case control study was carried out in the Department of Medicine comprising 50 newly diagnosed type 2 diabetes mellitus patients and 50 healthy controls. The HOMA IR method was used in the present study for estimation of insulin resistance as it is simple and appropriate. **Results:** median value of fasting plasma insulin in cases was 7.45 μ U/ml with mean 10.53 \pm 9.42 μ U/ml while in control was 7.19 with mean 7.43 \pm 2.26 μ U/ml (p value 0.025856) and of fasting plasma glucose was 146 mg/dl with mean 164.12 + 54.43mg/dl and controls had median 112 with mean 110.6 + 7.07mg/dl (p value 0.000000). The median value of HOMA IR score is 2.91 in cases with mean value of 4.15 \pm 3.56 and controls of 1.97, mean 2.03 + 0.64 (p value .000072). The most prevailing complications were retinopathy 26%(13,p<0.01) and neuropathy26%(13,P<0.01). **Conclusion:** HOMA-IR score in present study was higher, it indicates that IR was higher in Patient of T2 DM in Gwalior Chambal zone as compared to other countries and high score is associated with increase risk of diabetic retinopathy, neuropathy, nephropathy, CAD, Peripheral vascular disease.

Keywords: HOMA-IR, insulin resistance, type 2 diabetes, nephropathy, neuropathy

Introduction

Type-2 diabetes mellitus is a heterogeneous disorder characterized by chronic hyperglycemia due to dynamic interactions between varying defects of insulin secretion and insulin resistance. Either of these defects may be the predominant feature in a particular case [1]. 29.1 million people or 9.3% of US populations have diabetes in which diagnosed is 21.0 million and undiagnosed is 8.1 million people [2]. In adults type 2 DM accounts for about 90-95% of all diagnosed cases of diabetes.

It usually begins with insulin resistance, a disorder in which the cells primarily with in the muscles, liver, and fat tissue do not use insulin properly [2]. Type 2 diabetics have achieved pandemic proportions and it arises because insulin production is inadequate relation to demand of the body [3]. The hemostasis model assessment- estimated insulin resistance (HOMA-IR)

developed by Matthews et al has widely used for the estimation of insulin resistance in the research [4]. Martins *et al* [5] established that insulin resistance precedes and strongly predicts the development of type 2 diabetes mellitus among whites in the United States.

There is paucity of such studies in India. At present there is no exact cut off value of insulin resistance by HOMA in various studies among Indians. In the absence of local reference data for HOMA-IR score, we studied the insulin resistance in 50 patients of type-2 diabetes mellitus and normal healthy controls, to find out the insulin resistance value in type-2 diabetes mellitus patients and controls in Gwalior Region.

Thus, estimation of insulin resistance was helpful in detection of early complications and selecting the treatment options. Hence the present study was planned.

Manuscript received: 4th Aug 2013

Reviewed: 16th Dec Aug

Author Corrected: 29th Aug 2013

Accepted for Publication: 25th Sep 2014

Material and Methods

The present study was a prospective case control study conducted in the Department of Medicine, G.R. Medical College and J.A. Group of Hospitals, Gwalior. Fifty newly diagnosed type 2 diabetes mellitus patients and 50 healthy controls were studied.

Inclusion criteria: American Diabetes Association criteria have been used for selecting the newly diagnosed type-2 diabetes mellitus patients [6].

Exclusion criteria: Patients receiving drugs that alter the insulin sensitivity

Oral hypoglycemic agents (Insulin, β agonist, Prazosin, Diuretics, Steroids, OCP's), Condition associated with insulin resistance (PCOD, Thyrotoxicosis, Congestive cardiac failure, Chronic renal failure, Cirrhosis, Pregnancy), Hypertension (JNC – 7 stage I hypertension and stage II hypertension).

The volunteer study subjects, who satisfied the inclusion and exclusion criteria, were educated regarding the study, its aims and objectives. If they were willing to participate in the study, an informed consent was obtained and the subject taken into the study.

Controls: 50 healthy age and sex matched volunteers who had no personal or family history of diabetes mellitus, hypertension were recruited to serve as controls. Exclusion criteria were clinical evidence of any illness, personal or family history of Diabetes Mellitus, hypertension, current use of any form of medication.

Collection of data: All patients and controls were subjected to detailed history and physical examination

HOMA-IR was calculated using formula: HOMA IR) =

$$\frac{\text{Fasting plasma glucose (mg/dl)}}{18} \times \text{Fasting plasma insulin} = 22.5$$

The figure 22.5 in equation brings the insulin resistance values to one (Insulin sensitivity of 100%) of normal subject.

Statistical Analysis

Statistical analysis was done by calculation of range, median, mean, standard deviation, percentage, odds ratio, chi square test and p value. The statistical software SPSS 10.0 was used for the analysis of the data and Microsoft word and excel have been used to generate graphs, tables etc.

and investigations. Information on age, sex and anthropometrics waist circumference, waist hip ratio, height, weight, BMI [wt. (kg)/ ht (mtr²)] and ABI (was calculated using mercury sphygmomanometer in both case and control) measures were obtained from all cases and control subjects.

Patients were subjected to fundus examination to find out any diabetic retinal abnormalities.

Fasting (overnight 8 hrs) and postprandial (2 hrs) venous plasma glucose was determined by glucose oxidase method using glucose auto analyzer. Concentrations of total cholesterol, triglyceride HDL, LDL and cholesterol were determined by enzymatic kinetic method using an auto analyzer. Renal function test viz. blood urea & serum creatinine were done. Urine routine & microscopy and urine for microalbumin were also determined.

The serum plasma was stored at 20°C until assayed. Corresponding specific insulin concentration was determined by radioimmunoassay (RIA) using a human specific antibody RIA kit ECG was done..

Calculation of insulin resistance by HOMA

The HOMA method developed in 1985 by **Matthews and co-workers** was used in this study as it is simple and appropriate to developing countries where dynamic studies like the euglycemic glucose clamp technique [7], though the gold standard may not be feasible due to the degree of sophistication and cost of equipment necessary. Recently resistance in diabetic patients has been the focus of much attention [7,8,9,]. A significant correlation has been reported between the insulin resistance index calculated by HOMA and the hyperinsulinemic-euglycemic clamp (clamp IR) [7,10].

Results

Table No 1: Age wise distribution of cases

Age (in years)	No. of Cases	%
31-40	09	18%
41-50	18	36%
51-60	20	40%
>61	03	06%
Total	50	100

In the present study, patients were selected from 30 years to 70 years of age, majority of patients being in 50-60 years age group (40%). The average mean age for the studied cases was 49.98 ± 8.32 year & mean age of controls was 49.98 ± 8.32 years.

Table No 2: Insulin Resistance by HOMA-IR Score of cases & controls

Character	Cases	Controls	P-value
FPI (microunit/ml)			
Range	0.92-48.47	3.9-15.51	0.025856
Median	7.45	7.19	
Mean \pm SD	10.53 ± 9.42	7.43 ± 2.26	
FPG (mg/dl)			
Range	96-371	90-119	0.000000
Median	146	112	
Mean \pm SD	164.12 ± 54.43	110.6 ± 7.07	
HOMA-IR Score			
Range	0.22-18.77	1.08-4.4	0.000072
Median	2.91	1.97	
Mean \pm SD	4.15 ± 3.56	2.03 ± 0.64	

The above table shows the median value of fasting plasma insulin in cases was $7.45 \mu\text{U/ml}$ with mean $10.53 + 9.42 \mu\text{U/ml}$ while median value of fasting plasma in control was 7.19 with mean $7.43 + 2.26 \mu\text{U/ml}$ which is statistically significant (p value 0.025856).

The median value of fasting plasma glucose was 146 mg./dl with mean $164.12 + 54.43 \text{ mg/dl}$ and controls had median 112 with mean $110.6 + 7.07 \text{ mg/dl}$ which is statistically highly significant (p value 0.000000).

Mean value of HOMA-IR was significantly high in cases as compared to controls.

Table No 3: Co-relation of Complications on the basis of HOMA-IR

Complications	HOMA-IR		P-Value
	≤ 3.31	> 3.31	
Retinopathy Mean ± SD (n= No. of cases)	1.93 ± 0.67 (n=6)	9.3 ± 5.12 (n=7)	0.0051
Nephropathy Mean ± SD (n= No. of cases)	1.77 ± 0.82 (n=6)	7.18 ± 3.29 (n=5)	0.00349
Neuropathy Mean ± SD (n= No. of cases)	1.8 ± 0.69 (n=5)	5.64 ± 2.1 (n=8)	0.002467
CAD Mean ± SD (n= No. of cases)	2.06 ± 1.04 (n=2)	5.76 ± 0.8 (n=3)	0.01
Risk of PVD Mean ± SD (n= No. of cases)	1.74 ± 0.27 (n=2)	5.68 ± 0.1 (n=4)	0.000009

All complications were significantly higher in patients with HOMA IR >3.31. In the present study, most common complications in type 2 DM were retinopathy & neuropathy (26% each) followed by nephropathy in 22% cases, CAD in 10% cases and risk of PVD in 12%.

Table No 4: Relationship between Albumin/Creatinine Ratio & HOMA-IR

Alb./Cr. Ratio (mg/g)	HOMA-IR		P-value
	≤ 3.31	> 3.31	
ND - < 30 Mean ± SD (n= No. of cases)	1.97 ± 0.78 (n=22)	6.95 ± 3.92 (n=17)	0.000001
30-300 Mean ± SD (n= No. of cases)	1.77 ± 0.82 (n=6)	6.02 ± 2.55 (n=4)	0.004571
>300 Mean ± SD (n= No. of cases)	- -	11.48 ± (n=1)	-

Above table shows that most of the patients had albumin creatinine ratio <30mg/g. Out of 39 patients, 17 patients had HOMA IR >3.31. 11 patients had albumin creatinine ratio >30mg/g, of which 5 patients had HOMA IR >3.31.

(In present study, 39 patients had normal albumin/creatinine ratio (<30mg/dl) while 11 patients showed albumin/creatinine ratio >30mg/dl. Out of 39 patients having normal albumin/creatinine ratio, 17 patients had HOMA-IR >3.31 while out of 11 patients having disturbed albumin/creatinine ratio, 5 patients had insulin resistance.)

Discussion

The HOMA method developed by Mathew's & co-workers (1985)[11] was used in the present study for estimation of Insulin resistance as it is simple and appropriate. The HOMA method has been re-validated as a reliable method to assess insulin resistance in clinical practice as the HOMA IR score is shown to closely mirror the insulin resistance obtained by euglycemic clamp technique in assessment of insulin resistance (BONORA E et-al 2000)[7]. At present there is no exact cut off value of HOMA available in India. The present study was undertaken to find out insulin resistance value in T₂ DM patients and age & sex matched healthy controls.

Complications

In the present study, most common complications in type 2 DM were retinopathy & neuropathy (26% each) followed by nephropathy in 22% cases, CAD in 10% cases and risk of PVD in 12%.

Fasting plasma glucose, Fasting plasma Insulin and Insulin resistance

Mean value of fasting plasma insulin in cases was found to be $10.53 \pm 9.42 \mu\text{U/ml}$ while in controls $7.43 \pm 2.26 \mu\text{U/ml}$ with p value (0.025) which is statistically significant as shown in table no.12. Adamu G Bakari et al. (2005)[12] study found mean FPI $4.20 \pm 1.78 \mu\text{U/ml}$ in 40 T₂ DM patients, Vijay Vishwanathan et al (2010)[13] found mean FPI $46.1 \pm 2.5 \mu\text{U/ml}$ in controls in their study.

In the present study, mean FPI in cases was found to be higher than other studies i.e. may be marker of Insulin resistance. Mean Fasting plasma Glucose in cases was $164.12 \pm 54.43 \text{ mg/dl}$ while in controls it was $110.6 \pm 7.07 \text{ mg/dl}$ with P value 0.000 and this difference is statistically significant.

Mean HOMA IR Score in studied cases was 4.15 ± 3.56 & mean HOMA IR score in controls was 2.03 ± 0.64 with P value 0.000072 which was statistically highly significant. It means that Insulin resistance was found in type 2 DM patients.

HOMA IR in cases found to be mean 4.15 ± 3.56 . Adamu G et al (2005)[12] found mean HOMA-IR 1.73 in diabetic patients, Akira et al (2001)[14] found mean HOMA IR 2.04 ± 1.56 in 55 type 2 DM patients. Bonora et al (2000)[7] found mean HOMA-IR of 2.06 ± 0.14 in non diabetic normal population. Enzo Bonora et al (2007)[15] reported HOMA-IR of 2.5 in normal subjects. Hui- Qi Qu, et al (2011)[16] study showed that the best cut off of HOMA-IR for identifying those with insulin resistance is 3.80. HOMA-IR score in present study was higher than previous studies it indicates that IR was higher in Patient of T₂ DM in Gwalior Chambal zone as compared to other countries.

It is interesting that equation given by Mathew & co-workers [11] in 1985 shows that HOMA-IR 1 is equivalent to insulin sensitivity of 100% but in present study it was found that the mean value of HOMA IR score in cases was 4.15 ± 3.56 while in healthy controls it was 2.03 ± 0.64 so normal cut off value for HOMA-IR in healthy controls is difficult to specify.

Mathew & co-workers (1985)[11] said that normal value of HOMA-IR in healthy controls should be 1 but the present study shows that the mean value of HOMA-IR in healthy control was 2.03 & by adding two standard deviation the normal cut off value should be $2.03 \pm 2 \times 0.64$ equal to 3.31. It indicates that the normal cut off value of HOMA-IR in healthy persons in present study was 3.31. Previously HOMA-IR was calculated in healthy controls in various studies which are summarized in table from given below.

Table 5: showing comparison between various studies

Study	Age (yrs)	FPG	FPI	HOMA score
Adamu G Bakari 2005	49.4 ± 9.7	9.77 ± 4.03 (mmol/L)	4.2 ± 1.78 ($\mu\text{U/ml}$)	$1.73 \pm 1.4-7.6$
Enzo Bonora et al 2007	57.2 ± 11.2	5.5 (mmol/L)	75 (pmol/L)	$2.5 \pm 1.7-3.9$
Angelica Sink et al 2007	-	-	-	Considered HOMA <2 is normal
Srinivas et al Martha 2008	45.58 ± 8.56	76.83 ± 14.49 (mg%)	4.39 ± 2.68 ($\mu\text{U/ml}$)	0.89 ± 0.63
Our study	49.98 ± 8.32	110.6 ± 7.07 (mg/dl)	7.43 ± 2.26 ($\mu\text{U/ml}$)	2.03 ± 0.64

Research Article

Total 13 patients had diabetic retinopathy in studied group. Out of 13 patients, 7 patients of diabetic retinopathy had HOMA-IR score more than 3.31 while 6 patients had HOMA-IR less than cut off value with p value of 0.0051, so higher insulin resistance was statistically significant factor in the development of diabetic retinopathy.

In the present study total 11 patients had diabetic nephropathy, of which 5 patients with diabetic nephropathy had HOMA-IR >3.31 while 6 patients of diabetic nephropathy have HOMA-IR \leq 3.31 with P Value (0.00349) which was statistically significant factor. Thus, insulin resistance is associated with development of diabetic nephropathy.

Vijay Vishwnathan et al (2010)[13] also found high Insulin resistance in T2 DM patients associated with diabetic neuropathy they found that mean HOMA-IR significantly increases with progression of renal disease.

In the present study total 5 patients had CAD, of which 3 patients had HOMA-IR >3.31 while 2 patients had HOMA-IR \leq 3.31 with p Value (0.01) which statistically significant thus insulin resistance was a significant factor in development of CAD.

In the present study 13 patients had neuropathy, of which 8 patients had HOMA-IR >3.31 while 5 patients had HOMA-IR \leq 3.31 with p value 0.002467 which is statistically significant factor in development of neuropathy.

In the present study total 6 patients had PVD; of which 4 patients had HOMA-IR score more than 3.31 & 2 patients had HOMA \leq 3.31 which is statistically significant. Thus insulin resistance was significant factor in development of PVD.

Diabetic Nephropathy

Mean blood urea in cases was 31.96 ± 10.84 mg/dl and in controls 29.76 ± 6.56 mg/dl mean serum creatinine value was 0.89 ± 0.17 mg/dl in cases and 0.87 ± 0.113 mg/dl in controls (p value 0.49).

Albumin creatinine ratio is important indicator of nephropathy. Vijay Vishwanathan et al (2010)[13] studied insulin resistance in different stages of diabetic renal dysfunction.

They found that insulin resistance increases with worsening of renal function.

In present study, 39 patients had normal albumin/creatinine ratio (<30mg/dl) while 11 patients showed albumin/creatinine ratio >30mg/dl.

Out of 39 patients having normal albumin/creatinine ratio, 17 patients had HOMA-IR >3.31 while out of 11 patients having disturbed albumin/creatinine ratio, 5 patients had insulin resistance.

Conclusions

Mean value of HOMA-IR was significantly high in cases as compared to controls. In present study the normal cut off value for HOMA IR was 3.31. 44% type 2 DM patients had insulin resistance (HOMA IR >3.31) while 4% controls had insulin resistance (HOMA IR >3.31).

In day to day practice clinicians must think about insulin resistance in diabetic patients. As insulin resistance is an independent risk factor in diabetic patients in addition to all well established risk factors i.e. CAD, Hypertension, and Obesity.

It should be measured in all the diabetic patients because it is cheap and easily measurable from FPI and fasting blood sugar level.

Its measurement will help to prevent the development of various complications of diabetes at early stages.

Funding: Nil

Conflict of interest: None, **Permission from IRB:** Yes

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How to cite this article?

Purohit V, Tiwari V. Study of Insulin Resistance in Type 2 Diabetes Mellitus by Homa-IR Score. *Int J Med Res Rev* 2015;3(1):3-9. doi:10.17511/ijmrr.2015.i1.02

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