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Original Research Article

Estimation of Fasting Plasma Glucose, Fasting Insulin Levels and Insulin Resistance in Metabolic Syndrome

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ABSTRACT

Introduction: A group of metabolic disorders like central obesity, insulin resistance, increased insulin level, impaired glucose homeostasis, dyslipidemia, raised blood pressure and low grade chronic inflammation is defined as metabolic syndrome. It is a complex disorder and an emerging clinical challenge which is associated with 2 fold increase in CVD risk and 5 fold increase in T2DM.

Materials and methods: Hundred clinically diagnosed patients with Metabolic Syndrome and fifty controls were selected for the study

Results: Fasting Plasma Glucose, Fasting Plasma Insulin, Mean HOMA-IR of patients with metabolic syndrome were significantly higher as compared to healthy controls. 61% of patients with metabolic syndrome were with severe insulin resistance consisting 38% of male and 23% of female. 18% cases were found to be with moderate insulin resistance including 11% male and 7% female. Whereas 21% of the patient with MetS were with normal insulin resistance. ROC Curve was analysed for HOMA-IR in predicting metabolic syndrome and specificity and sensitivity was calculated which came out to be87% and 100% respectively.

Conclusion: Diagnosing metabolic syndrome and assessing HOMA-IR shows the status of insulin resistance thereafter may guide in assessing the risk of development of T2DM and CVD in patients with metabolic syndrome.ROC curve further helps in early diagnosis of metabolic syndrome using a single parameter with specificity and sensitivity of 87% and 100% respectively which is more practical against the other criteria used for diagnosing metabolic syndrome.

Key words: *Metabolic Syndrome, Fasting Insulin, Insulin resistance, plasma Glucose.*

INTRODUCTION

A group of metabolic disorders like central obesity, insulin resistance, increased insulin level, impaired glucose homeostasis, dyslipidemia, raised blood pressure and low grade chronic inflammation is defined as metabolic syndrome. [1] The prevalence of MetS worldwide varies from less than 10% to 84%, depending upon the region, composition of the population studied with respect to age, sex, race, ethnicity etc. and the definition of the MetS used. [2,3] In context of India, the prevalence of metabolic syndrome is more in urban areas as compared to rural and it has been suggested by numerous surveys that one-third of the people have been suffering from metabolic syndrome. [4-6] The glucose homeostasis plays a crucial role in stimulation of insulin gene transcription and mRNA translation beside multiple factors. Blood glucose level beyond 70 mg/dl increase the protein translation and processing for the synthesis of insulin. Hypoglycaemic hormone (Insulin) and a number of hyperglycaemic hormones (glucagon, thyroid, PTH, epinephrine, nor epinephrine) maintain the glucose

homeostasis by making a balance between hepatic glucose production and peripheral glucose uptake for utilisation. Insulin plays a predominant role for the balanced glucose homeostasis. Under fasting condition, insulin levels are decreased and increases hepatic production of glucose inducing metabolic pathways like gluconeogenesis and glycogenolysis. It results in reduce glucose uptake in tissues and promoting mobilisation of stored precursors such as amino acids and free fatty acids (lipolysis) as well. Insulin is an anabolic hormone, which helps in the synthesis and storage of carbohydrate, fat and protein synthesis. Skeletal muscle is the major organ which utilizes the major amount of glucose under the influence of glucose whereas brain utilises glucose in an insulin independent fashion. [7] Inability of tissues to response the insulin or derangement in insulin signalling pathway with a characteristic feature of hyperinsulinemia is termed as insulin resistance. Causes of insulin resistance: Genetics, Chronic excess energy intake, Lack of exercise and physical activity, Stress, Chronic sleep deprivation, Pregnancy, Obesity, Chronic inflammation. [8] Insulin resistance is an essential feature of MetS which increases the risk in development of T2DM. [9]

The Homeostasis Model Assessment of IR (HOMA-IR) is globally used robust tool for alternate assessment of IR. HOMA-IR will be calculated as:

$$\text{HOMA} - \text{IR} = \frac{\text{Fasting plasma insulin (}\mu\text{IU/ml) x Fasting plasma glucose (mg/dl)}}{405}$$

Explanation of result was according to the category of Insulin resistance by HOMA-IR.as Normal (score of HOMA- IR <3); Moderate (score of HOMA- IR 3-5); Severe (score of HOMA- IR >5). [10] A huge number of publications have reported significant increased levels of insulin and HOMA-IR with other constituents of MetS in patients with MetS as compared to subjects without MetS. Numerous researchers have evidenced the positive correlation between obesity and insulin or obesity and HOMA-IR. [11-14]

Aims and objectives: The present study was conducted in the Department of Biochemistry in collaboration with Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala. The major aim and objectives of the conducted study were:1) To estimate Fasting Plasma glucose, Fasting plasma Insulin, in subjects with metabolic syndrome & healthy controls; 2) To evaluate insulin resistance (HOMA-IR) in subjects with metabolic syndrome and healthy controls.

MATERIALS AND METHODS

One hundred (100) clinically diagnosed patients with Metabolic Syndrome on the basis of NCEP ATP III with age above thirty (30) years of either sex, attending the OPD and wards of Department of Medicine of MMIMSR, Mullana, Ambala, were selected for the study. Fifty (50) subjects of either sex with age above thirty (30) years were selected to serve as controls.

RESULTS

We calculated the Mean Fasting Plasma Glucose, Mean Fasting Plasma Insulin, Mean HOMA-IR (Insulin Resistance), and t-Test between healthy controls and patients with metabolic syndrome. It was observed that Fasting Plasma Glucose of patients with metabolic syndrome (166.072±85.42 mg/dl) were higher as compared to healthy controls (86.58± 7.84 mg/dl) which was significant at 0.01 level. Fasting Plasma Insulin of patients with metabolic syndrome (20.268±11.479 µIU/ml) were higher as compared to healthy controls (5.624± 1.719 µIU/ml) which was significant at 0.01 level. Mean HOMA-IR of patients with metabolic

syndrome (8.747±7.968) was higher as compared to healthy controls (1.202 ± 0.389) which were significant at 0.01 level. (Table 1)

Table 1: Mean Fasting Plasma Glucose, Mean Fasting Plasma Insulin, Mean HOMA-IR (Insulin Resistance), and t-Test between healthy controls and patients with metabolic syndrome.

	Group	Mean	Standard deviation	*p*
Glucose (mg/dl)	Controls	86.580	7.8471	< 0.001
	Cases	166.072	85.4228	
Insulin (µIU/ml)	Control	5.624	1.7199	< 0.001
	Cases	20.268	11.4797	
HOMA-IR	Controls	1.2020	0.38966	<0.001
	Cases	8.7472	7.96898	

We categorised the Insulin resistance by HOMA-IR in patients with metabolic syndrome. It was observed that 61% of patients with metabolic syndrome were with severe insulin resistance according to HOMA –IR Score consisting 38% of male and 23% of female. 18% cases were found to be with moderate insulin resistance including 11% male and 7% female. Whereas 21% of the patient with MetS were with normal insulin resistance. (Table 2)

Table 2: Showing the category of Insulin resistance by HOMA-IR in patients with metabolic syndrome.

HOMA-IR Score	Normal Insulin Resistance (<3)		Moderate Insulin Resistance (3-5)		Severe Insulin Resistance (>5)	
	Male	Female	Male	Female	Male	Female
	9%	12%	11%	7%	38%	23%
Total	21%		18%		61%	
	100%					

Receiver Operating Characteristic (ROC) Curve was analysed for HOMA-IR in predicting metabolic syndrome. From the ROC curve analysis AUC (Area under cover) was found 0.945 which was significant at 0.01 level in prediction of metabolic syndrome from HOMA-IR. (Figure1, Table 3)

We calculated specificity and sensitivity. The criterion values and coordinates of the ROC curve showed that when HOMA-IR of 2.50 was selected as a cut-off point for predicting metabolic syndrome, it was found to have a sensitivity of 87% and specificity of 100%. (Table 4)

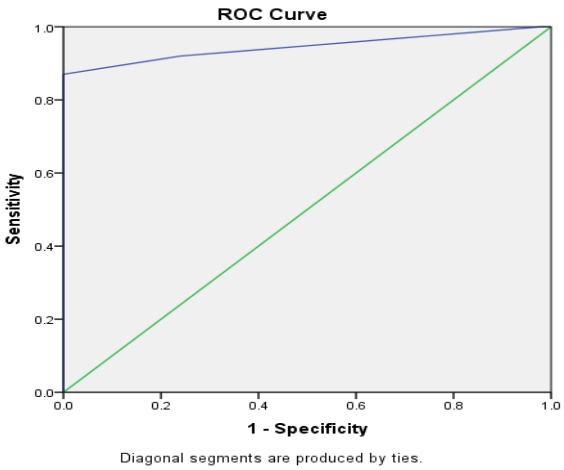

Figure 1: ROC curve for HOMA-IR

Table 3: Showing Area under the curve from ROC curve of HOMA-IR.

Area	Std. error	Significance	Asymptomatic 95% confidence interval	
			Lower bound	Upper bound
0.945	0.019	<0.001	0.909	0.982

Table 4: Criterion values and Coordinates of the ROC curve of HOMA-IR:

HOMA-IR	Sensitivity (%)	1-Specificity	Specificity (%)
0.5	100%	0.98	2%
1.5	92%	0.24	76%
2.50	87%	0.00	100%
3.50	75%	0.00	100%

DISCUSSION

Metabolic syndrome is a complex disorder and an emerging clinical challenge which is associated with 2 fold increase in CVD risk and 5 fold increase in T2DM. In the present study it was observed that Fasting Plasma Glucose of patients with metabolic syndrome were higher as compared to healthy control which was significant. The results is in agreement with Haddad N., [15] Naik et al., [16] Sigdel et al., [17] Guha et al. [18] and Siu PM. [19] Pre-diabetes (Hyperglycaemia but below that of clinical diabetes) is commonly associated with the metabolic syndrome whereas, diabetes mellitus is the morbidity of

metabolic syndrome. Insulin resistance is a common factor for hyperglycaemia in metabolic syndrome. Most persons with both conditions (pre-diabetes and metabolic syndrome) are obese. An increase in adipose tissue results in elevations of circulating free fatty acids (FFAs) and other "adipokines" where the latter appear to underlie both a pro-inflammatory state and a prothrombotic state. An increase in FFAs induces insulin resistance (IR) in muscle, which contributes to an elevation of plasma glucose. [20] In healthy people subjected to a euglycemic, skeletal muscle is the main tissue that accounts for ~80% of glucose uptake and is used for glycogen synthesis and glycolysis. Insulin signaling through IRS-1, phosphatidylinositol 3-kinase (PI3K)/ Akt is decreased in insulin resistance, ultimately decreasing the translocation of the glucose transporter GLUT4 to the plasma membrane and impaired insulin–stimulated glucose transport into the cell leading to hyperglycaemia. [21]

It was observed that Fasting Plasma Insulin of patients with metabolic syndrome was higher as compared to healthy controls which were significant. This is in accordance with study done by Allam-Ndoul et al., [22] Ghamarchehreh et al, [23] Kurl et al., [24] which observed significantly increased insulin levels in patients with metabolic syndrome. Hyperinsulinemia is the consequence of insulin resistance. The pancreas compensates by increasing the secretion of insulin into the bloodstream to overcome defects in peripheral insulin action in the early stages of insulin resistance. In response to this increased demand for insulin production, the β-cells hypertrophy may also take place leading to hyperinsulinemia. [25]

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) tool was used for the surrogate assessment of insulin resistance. [26] The present study demonstrated significantly ($p<0.001$) higher HOMA-IR in patients with metabolic syndrome (8.747±7.968) as compared to healthy controls (1.202 ± 0.389). This is in agreement with the findings of Barseem NF, [13] Shekhar et al., [27] and Gowdaiah et al. [28] The genetic mutations or defect in the molecules of the insulin signaling cascade causes the insulin resistance and T2D only in rare occasions. Lipid oversupply or obesity and alterations in substrate metabolism due to inactivity are central underpinnings of chronic tissue inflammation contributing to the manifestation of peripheral insulin resistance. [25] The accumulation of bioactive lipid species in peripheral tissues activate proinflammatory signaling pathways and novel Protein Kinase C (PKCs), [29,30] and they impair insulin signal transduction by modulating major phosphorylation events and important protein-protein interactions. Most of the impairments in muscle insulin action are caused by post receptor defects. Impaired insulin action at the level of IRS-1 caused by activation of stress kinases [e.g., c-Jun N-terminal kinase (JNK) and nuclear factor-κB (IκB) kinase (IKK)β] and impaired phosphorylation of IRS-1. [31-33]

According to HOMA–IR Score, it was observed in the present study that 61% of patients with metabolic syndrome were with severe insulin resistance (>5) consisting 38% of male and 23% of female. 18% cases were found to be with moderate insulin resistance (3-5) including 11% male and 7% female whereas 21% of the patients with MetS were with normal insulin resistance (<3). The observation from the present study demonstrates that though majority of patients with MetS were with severe insulin resistance and moderate insulin resistance there were also MetS patients who had normal insulin resistance. It concludes that only insulin resistance is not the merely cause of MetS. A number of publication supports that the majority of insulin resistance seen in MetS is obesity induced. [34-37]

Receiver Operating Characteristic (ROC) Curve was analysed for HOMA-IR in the present study for prediction of metabolic syndrome. From the ROC curve analysis AUC (Area Under Cover) was

found 0.945 which was highly significant ($p<0.001$). From the table of criterion values and coordinates of the ROC curve, when HOMA-IR level 2.50 was selected as a cut-off point for predicting metabolic syndrome, it was found to have a sensitivity of 87% and specificity of 100%. As compared, in study of Gayoso-Diz et al. [11] HOMA-IR cut-off values for MetS ranged from 2.07 (sensitivity, 0.72; specificity, 0.71) at 50 years to 2.47 (sensitivity, 0.44; specificity, 0.74) at 70 years.

Overall, the results of the present study demonstrated that plasma levels of glucose and insulin and HOMA-IR are altered in subjects with MetS clearly suggesting the presence of insulin resistance, inflammation, hypertension and atherogenicity which may be related to diabetes and CVD. However, the interplay of various hormones of adipose tissue and proinflammatory cytokines in the pathophysiology of MetS and leading to morbidities like diabetes and CVD is rather complex and needs further elucidation.

CONCLUSION

In conclusion, diagnosing metabolic syndrome and assessing HOMA-IR shows the status of insulin resistance thereafter may guide in assessing the risk of development of T2DM and CVD in patients with metabolic syndrome. Appropriate measures can be implemented in such high risk subjects in order to protect them from development of T2DM and CVD. Cut off values 2.50 for HOMA-IR obtained from ROC curve further helps in early diagnosis of metabolic syndrome using a single parameter which is more practical against the other criteria used for diagnosing metabolic syndrome where maximum parameters are analyzed.

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