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Homa-Ir and Ratios of Tg/Hdl and Tc/Hdl as Indicators of Insulin Resistance in Patient with Metabolic Syndrome and Type 2 Diabetes Mellitus

KEYWORDS: Insulin resistance (IR), triglyceride (TG), high density lipoprotein (HDL), metabolic syndrome (MS),Type 2 diabetes mellitus (T2DM), HOMA-IR.

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ABSTRACT *Objectives: The aim of the study was to compare the ratios of TG/HDL and TC/HDL with HOMA-IR as indicators of Insulin Resistance in patients with Metabolic Syndrome and Type-2 Diabetes Mellitus.*

Materials and methods: Total 120 patients were recruited in the study after obtaining informed consent. They were divided in three groups. Group I included healthy individuals as control (n = 40), Group II included patients with metabolic syndrome (MS) (n = 40) and Group III included patients withtype 2 diabetes mellitus (n = 40).

Result: There was significant difference between the anthropometric parameters and lipid parameters in control and study groups (p < 0.05). Significant positive correlation was seen between the regression model of HOMA-IR and TC/HDL(p<0.009) and HOMA-IR and TG/HDL(p<0.01) in Metabolic Syndrome patients.Alsosignificant positive correlation was seen between the regression model of HOMA-IR and TG/HDL and HOMA-IR and TC/HDL (p≤0.001) in patients withtype-2 diabetes mellitus.

Conclusion: We propose that the TG/HDL and TC/HDL ratios serve as an easily available and economic marker for the busy clinicians to identifying insulin resistance in metabolic syndrome patients. The combination of these evaluated markers may identify a group of patients with a more marked risk for insulin resistance and cardiovascular disease risk.

1. INTRODUCTION:

Metabolic syndrome is characteristically defined as a clustering condition of cardiovascular risk factors Including hyperglycemia, dyslipidemia, hypertension, and central obesity [1]. Its occurrence is strongly associated with increased risk in the development of type 2 diabetes mellitus and cardiovascular disease.[2]

Metabolic syndrome can be identified by many ways that are IDF, WHO, NCEP ATP III. The NCEP definition has higher sensitivity than the modified WHO definition. Hence the most commonly accepted is NCEP ATP III.[3]

ATP III considered the "obesity epidemic" as mainly responsible for the rising prevalence of metabolic syndrome. Obesity contributes to hypertension, high serum cholesterol, low HDL cholesterol, and hyperglycemia, and it otherwise associates with higher CVD risk. Abdominal obesity especially correlates with metabolic risk factors.[4]

Many of its features are associated with insulin resistance. It is typically defined as decreased sensitivity or responsiveness to metabolic actions of insulin, such as insulin-mediated glucose disposal and inhibition of hepatic glucose production (HGP).[5]

It is estimated that around 20-25 percent of the world's adult population have the metabolic syndrome and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome.[6] Epidemiologists in India and international agencies such as the world health organization (WHO) have been sounding an alarm on the rapidly rising burden of CVD for the past 15 years and will be the largest cause of disability and death in India, with 2.6 million Indians predicted to die.[7,8]

In addition, people with metabolic syndrome have a five-fold greater risk of developing type 2 diabetes.[6] They would add to the 382 million people worldwide who already have diabetes, one of the most common chronic diseases worldwide and the fourth or fifth leading cause of death in the developed world. A further 316 million with impaired glucose tolerance are at high risk from the disease – an alarming number that is set to reach 471 million by 2035.[9] The recently published ICMR-INDIAB national study reported that there are 62.4 million people with diabetes and 77 million people with pre-diabetes in India.[10]

Insulin resistance occurs when cells in the body (liver, skeletal muscle and adipose/fat tissue) become less sensitive and eventually resistant to insulin, the hormone which is produced by the beta cells in the pancreas to facilitate glucose absorption. This leads to hyperglycemia.[11, 5]

Persistence or prolonged hyperglycemia will lead to development of diabetes mellitus over a period of time. Type 2 diabetes mellitus is a heterogeneous condition characterized by the presence of both impaired insulin secretion and insulin resistance. Type 2 diabetes mellitus makes up about 90% of the diabetic population. Time between insulin resistance and diabetes mellitus development is characterized by conditions like dyslipidemia.

IFG and IGT represent intermediate states of abnormal glucose regulation that exist between normal glucose homeostasis and diabetes. The transition from the early metabolic abnormalities that precede diabetes, impaired fast-

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ing glucose (IFG) and impaired glucose tolerance (IGT), to diabetes may take many years, however, current estimates indicate that most individuals (perhaps up to 70%) with these pre-diabetic states eventually develop diabetes.(12)

Currently, there are several direct and indirect methods to assess insulin resistance. One of the most widely used validation measures for IR is the Homeostasis Model Assessment–Insulin Resistance (HOMA–IR) index [12], which uses the determination of fasting insulin and glucose using the formula:

HOMA–IR = fasting insulin

(μU/mL) x fasting glucose (mg/L)/405

Other possible indicators are the lipid ratios such as TG/HDL and TC/HDL ratios.These ratios are reliable marker for estimating the insulin resistance.

Insulin resistance and dyslipidemia leads to increased secretion of triglyceride and decreased HDL cholesterol and increased concentration of small dense LDL–cholesterol particles. [13] Hence, the TG/HDL and TC/HDL cholesterol ratios are strong correlate of insulin resistance and type 2 diabetes mellitus.

Elevated TG/HDL and TC/HDL ratios are associated with the presence of IR, along with the more atherogenic lipid profile, higher waist-hip ratio, and higher BMI. Hence determining the ratio will help significantly to relate IR, metabolic syndrome and type 2 diabetes mellitus. Comparing them will help predict the better surrogates of IR.[14] Therefore this study was planned to assess and compare TG/HDL and TC/HDL ratios as indicator of insulin resistance in patients with metabolic syndrome and type 2 diabetes mellitus.

2. MATERIALS AND METHODS:

The present study was approved by Institutional ethics review committee. A total of 120 subjects between age group of 30 to 70 were enrolled for the study after obtaining their informed consent. The subjects were divided into three groups**.** Group I included 40 healthy individuals, Group II included 40 metabolic syndrome patients as per NCEP ATP III criteria which is based on the presence of three or more of the risk factors such as: Waist circumference (WC): men > 102 cm (40 in); women > 88 cm (35 in); Triglycerides ≥150 mg/dl; HDL-C: men < 40 mg/dl; women < 50 mg/dl; Blood pressure ≥130/≥ 85 mmHg; Fasting glucose ≥110 mg/dl. and Group III included 40 Type-2 Diabetes mellitus patients as per WHO criteria that is 2 hour glucose ≥200 (mg/dl), Fasting ≥126 (mg/dl) and HbA_{1c} ≥6.5 DCCT %. All the subjects were matched for age, gender and were nonsmokers, non-alcoholic and of same socio-economic status. Subjects with chronic diseases of kidney, liver, patients of cancer and endocrinological disorder other than diabetes were excluded from the study.

Measurements of height and weight were done with the subjects standing, without shoes and with light clothing. BMI was calculated as weight in kg divided by height in meter squared. WC was measured at the level of the umbilicus with a tape in centimeter scale.

Blood samples were obtained from vein under conditions of 12 hour of fasting. Fasting plasma glucose, TG, HDL cholesterol level was measured by enzymatic technique on fully automated analyzer. Fasting plasma insulin was measured by ELISA technique. Insulin resistance was measured by formula multiplying fasting plasma insulin (FPI) by fasting plasma glucose (FPG), then dividing by 405.

HOMA-IR = (FPI×FPG)/405

2.1 STATISTICAL ANALYSIS

Data are presented as means ± SD, student t-test was used to compare BMI, W/H ratio, TG, HDL between patients and controls. The correlation of HOMA and TG/HDL and TC/HDL was determined by Pearson correlation coefficient and scatter diagram was obtained. P values < 0.05 were considered statistically significant.

3. RESULTS

Table 1 shows anthropometric and clinical characteristics of study and control groups. There were significant differences in the values of BMI, W/H Ratio, TG and HDL level in study and control groups $p < 0.01$. Correlation of HOMA-IR with TG/HDL and TC/HDL was done in patients with Metabolic Syndrome and Type-2 Diabetes mellitus.

The scatter graph 1 and 2 shows that there exist significant strong positive correlation between HOMA-IR and TC/HDL ($r = 0.163$) ($p<0.01$) and significant strong positive correlation between HOMA and TG/HDL ($r = 0.168$) ($p \leq 0.009$) in Metabolic Syndrome.(table 2)

Also it was seen that there was a significant ($r = 0.31$) ($p \leq 0.0001$) strong positive correlation between HOMA-IR and TG/HDL and significant ($r = 0.42$) ($p \leq 0.0001$) strong positive correlation between HOMA-IR and TC/HDL in type-2 diabetic group. (Table 3, graph 3 and 4).

Table 1. Descriptive statistics for different groups

Parameters	Control group III Healthy individual	Metabolic syndrome group I	Type-2 diabetes mellitus group II	P- value
BMI	22.78 ± 1.88	29.09 ± 3.04**	29.02 ± 4.43**	P ≤ 0.01
W/H Ratio	0.83 ± 0.018	0.99 ± 0.056**	0.98 ± 0.057**	P ≤ 0.01
Triglyceride (TG)	114.1 ± 28.073	182.6 ± 29.10*	191.95 ± 57.22*	P ≤ 0.05
High density lipoprotein (HDL)	41.83 ± 10.42	37.35 ± 5.15*	35.6 ± 7.10*	P ≤ 0.05

Data represented as mean ± SD

Table 2: Correltion of HOMA-IR with TG/HDL, TC/HDL in patient with Metabolic Syndrome

		TG/HDL	TC/HDL
HOMA_IR	Pearson Correlation	0.410**	0.404**
	p-value	0.009	0.010
	N	40	40
**. Correlation is significant at the 0.01 level (2-tailed).			

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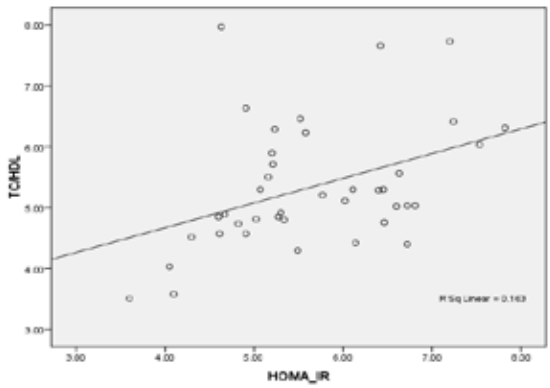
Graph 1: Correlation between TC/HDL-C ratio and HOMA-IR in patient with metabolic syndrome



Graph 2: Correlation between TG/HDL-C ratio and HOMA-IR in patient with metabolic syndrome

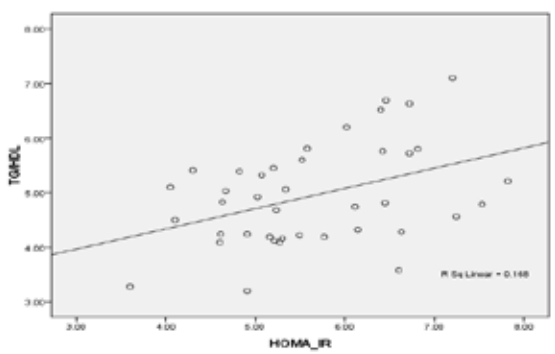
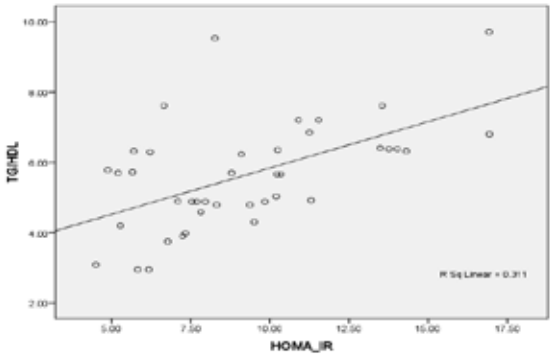


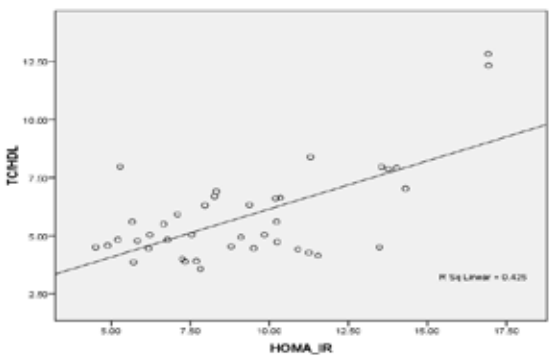
Table 3: Correltion of HOMA- IR with TG/HDL and TC/HDL in patients with Type-2 Diabetes mellitus

		TG/HDL	TC/HDL
HOMA_IR	Pearson Correlation	0.558**	0.652**
	p-value	< 0.0001	< 0.0001
	N	40	40
**. Correlation is significant at the 0.01 level (2-tailed).			

Graph 3 Correlation between TG/HDL-C ratio and HOMA-IR in type-2 diabetes mellitus



Graph 4: Correlation between TC/HDL-C ratio and HOMA-IR in type-2 Diabetes mellitus



4. DISCUSSION:

HOMA-IR being the widely accepted gold standard for IR, however our study aimed to develop TG & HDL-C and TC & HDL as a simple predictive model as a clinical tool for evaluation of insulin resistance. In clinical settings, it would be useful to identify individuals with insulin resistance using only routinely collected blood test results such as triglyceride, total cholesterol and high-density lipoprotein cholesterol. Hence, we proposed the prediction of insulin resistance by the ratio of TG & HDL and TC & HDL.

Metabolic Syndrome patients showed significant strong positive correlation between HOMA-IR and TC/HDL ($p<0.009$) and HOMA –IR and TG/HDL($p<0.01$) as shown in table 2, graph 1 and 2. Jeppesen J et al in 1997, evaluated that TC/HDL-C ratio, TG/HDL-C, ratio can be used as the markers of insulin resistance and CVD risk in T2D patients.[16]

Alos it was seen that there was significant ($p \leq 0.001$) strong positive correlation between HOMA-IR and TG/HDL and HOMA-IR and TC/HDL in patients with the type-2 diabetes mellitus group, as shown in table 3, graph 3 and 4.

Our study is in accordance to **Salzar** et al. (2013), **Morato** et al (2010) and **Brehm** et al (2014), who demonstrated positive correlation between TG/HDL ratios and insulin resistance, confirming that the TG/HDL ratio predicts insulin resistance in metabolic syndrome. [17,18,19] But an independent study by **Knight** et al (2011), stated that TG/HDL ratio fails to predict Insulin resistance in African American women.[20]

5. CONCLUSION

The results of our study showed elevated TG/HDL ratio

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and the TC/HDL ratio. One of the most widely used validation measures for IR is the HOMA-IR index, which uses the determination of fasting insulin and glucose; however, this is mainly used for clinical research purposes. For daily clinical practice, it is necessary to use other easily applied measurements in the general population. Therefore we propose that the TG/HDL and TC/HDL ratios serve as an easily available and economic marker for the busy clinicians to identifying insulin resistance in metabolic syndrome patients. The combination of these evaluated markers may identify a group of patients with a more marked risk for insulin resistance and cardiovascular disease risk.

Limitations:
Further studies are needed that demonstrate consistency in the association between TG/HDL and TC/HDL ratios, IR and various metabolic disorders that comprise the MetS and CVD. In addition, future studies can determine the use of this ratio as a marker of IR, which requires an appropriate study design and adequate sample size to validate.

CONSENT: Authors declare that written informed consents were obtained from patients before their participation in the study.

ETHICAL APPROVAL: All authors hereby declare that approval from Institutional ethics review committee was obtained and study was carried out as per standards.

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