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Research Article

Evaluation of triglyceride: HDL-C ratio and Non-HDL-C as harbingers of increased cardiovascular risk in metabolic syndrome

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ABSTRACT

Background: Metabolic syndrome is an aggregate of conditions that together increases the risk of developing cardiovascular disease and type 2 diabetes mellitus. Dyslipidemia consisting of elevated triglyceride, decreased HDL, and altered triglyceride to high density lipoprotein- Cholesterol (TG/HDL-C) ratio is useful in predicting cardiometabolic risk and insulin resistance. The present study aimed to compile further evidence for clinical utility of TG/HDL-C ratio and Non HDL-C as simple, cost effective tools for early identification of cardiovascular disease risk in metabolic syndrome.
Methods: This study was carried out with hundred subjects. Fifty of these subjects were diagnosed with metabolic syndrome according to National Cholesterol Education Program Adult Treatment Panel III; while other fifty were age and gender matched healthy control subjects.
Results: The impact of cardiometabolic markers on metabolic syndrome was assessed separately in men and women by applying Mann Whitney 'U' test. Study showed highly significant increase in TG, HDL, TC/TG and TG/HDL-C ratio in women compared to men with $p<0.01$. The odds ratio of TG/HDL for women showed the highest ratio of 6, 95% CI (1.5225 to 23.6401) $p=0.006$ compared to men 4.9583, 95% CI (1.0088-24.3711), $p=0.004$.
Conclusions: This study demonstrated that TG/HDL-C ratio and Non HDL-C are strongly associated with metabolic syndrome in urban population. In comparison, TG/HDL-C is a better predictor of metabolic syndrome than non-HDL-C.

Keywords: Metabolic syndrome, Triglyceride: HDL-C ratio, Non- high density lipoprotein cholesterol

INTRODUCTION

Metabolic syndrome is an entity comprising of cardiometabolic risk factors, viz. central obesity, glucose intolerance, hyperinsulinemia, low High Density Lipoprotein cholesterol (HDL-C), high triglycerides (TG) and hypertension.[1]

In south India, the prevalence of metabolic syndrome is estimated to be 23.2%, 18.3% and 25.8% according to the WHO, ATP III and IDF criteria respectively.[2] There is a predilection of metabolic syndrome and associated complications in south Asians. South Asia is the most densely populated geographic region in the world and thus, contributes to the high burden of metabolic syndrome in the world.[3] The components of metabolic syndrome reflect the metabolic abnormalities that place an emphasis on ectopic fat accumulation and associated cardiometabolic risk factors.

These components are continuous variables that can be categorized to define populations at particularly high risk which provides a pragmatic approach for clinicians,

researchers and policymakers to address the problem of metabolic syndrome in the community. The focus is on early detection and treatment of individuals with abnormal levels of components with appropriate lifestyle changes. Early identification still poses a challenge as the cardiometabolic risk factors may not be perceived to warrant treatment as per the pharmacological guidelines to initiate drug therapy. This is especially true with the conventional lipids and lipoproteins panel which should be viewed with the discerning eye as simple calculations of certain lipid ratios could perform better than the individual lipids in cardiometabolic risk prediction.

Current research has shown that triglyceride to high density lipoprotein cholesterol (TG/HDL-C) ratio to be useful in predicting cardiometabolic risk and insulin resistance.[4,5] This ratio would be simple yet effective tool for screening, initiating appropriate treatment (such as statins) and monitoring. However, there is paucity of data demonstrating the same in India population.

Non HDL-C is a calculated lipid parameter and collectively represents all of the potentially atherogenic lipids. In a recent study conducted to elucidate the association of non HDL-C in metabolic syndrome subjects with coronary artery disease (CAD) demonstrated the increased propensity of CAD in subjects with elevated non HDL-C.[6]

The aim of the present study is to compile further evidence for clinical utility of TG/HDL-C ratio and non HDL-C as simple, effective tools for early identification of metabolic syndrome and as harbingers of cardiovascular disease.

METHODS

The study was approved by the ethical committee of the institute and an informed consent was obtained from all subjects who took part in the study.

Study comprised of metabolic syndrome patients attending the outpatient and inpatient of Medicine department of Victoria hospital and Bowring and Lady Curzon hospitals attached to Bangalore Medical College and Research Institute, Bangalore. All patients were diagnosed according to National Cholesterol Education Program, Adult Treatment Panel III criteria and it requires the presence of 3 or more of the following:

- Fasting blood glucose ≥110 mg/dl
- Serum triglyceride ≥150mg/dl or being on lipid lowering therapy
- Serum HDL <40 mg/dl in men and <50 mg/dl in women or being on antilipidemic therapy
- Blood pressure ≥130 mmHg systolic and ≥85 mmHg diastolic or being on antihypertensive therapy and
- Waist circumference >102 cm in men and >88 cm in women.

Patients with following history were excluded:

- History of ischemic heart disease
- History of alcohol intake and smoking
- Renal disease
- Acute infectious/inflammatory conditions.

After consulting statistician, sample size was estimated to be 100, with 50 cases and 50, age and gender matched healthy controls. Selected subject's blood samples were collected with all aseptic precautions. 5 ml of blood was collected from median cubital vein. Collected blood was allowed to clot for 30 minutes in a clean dry test tube and was subjected to centrifugation to separate the serum. The serum samples were stored in Deep freezer at -80^{0}C till they were analyzed.

The glucose (hexokinase method), Triglycerides (glycerol phosphate oxidase peroxidase method), Total Cholesterol (Cholesterol oxidase peroxidase method) were measured in serum by the standard kits. For the estimation of serum High Density Lipoprotein Cholesterol (HDL-C) and the Very Low Density Lipoprotein (VLDL) was measured by the precipitating reagent (Dextran sulfate and Magnesium ion) and the remaining HDL-C fraction was measured by the cholesterol oxidase method. The LDL-C was calculated by the Friedewald formula.[12] {LDL-C = TC – (HDL-C + TG/5)}. The Non-HDL- C can be calculated as total cholesterol minus HDL-C, the TG: HDL-C ratio can be calculated by dividing the triglycerides with HDL-C.

Statistical analysis

Statistical analysis was performed by using SPSS version 16.0. Chicago, SPSS Inc. Results on continuous measurements are presented on Mean ± SD. Mann Whitney 'U' test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups. Fisher Exact test has been used to find the significance of study parameters on categorical scale between two groups. Chi-Square analysis was used to calculate the odds ratio and associated 95% confidence intervals for the derangement in lipid ratio TG: HDL-C of men and women with metabolic syndrome.

RESULTS

The clinical characteristics of the study population are shown in Table 1. The current study comprises of 50 metabolic syndrome cases and 50 age and gender matched healthy controls. The results are tabulated and statistically analyzed. BMI and waist circumference (WC) are the two important anthropometric measurements among the various definitions of metabolic syndrome. In this study, mean±SD of BMI and WC were significantly higher in cases compared to controls with $p<0.01$. Table II represents comparison of lipid profiles of cases and controls. The study showed TG, HDL,

VLDL, and TG: HDL-C ratio was significantly high in cases compared to controls with p<0.001. In case of non HDL-C, showed a suggestive significance of p=0.2. Table III compares the cardio-metabolic risk factors in men with metabolic syndrome and their age matched controls by Mann Whitney 'U' test. Out of the 100 participants, 35 were men, among them, 20 were metabolic syndrome cases and 15 were controls. Comparison of the lipid parameters revealed a moderate significance with respect to total cholesterol, TG, HDL, LDL, non-HDL whereas TG: HDL ratio showed statistically significant increase in metabolic syndrome cases compared to controls with p<0.05 suggesting the predisposition of such individuals to overt diabetes mellitus and CVD.

Table 1: Clinical characteristics of the study population.

	Controls (n=50)	Metabolic syndrome (n=50)	'p' value
Age (years)	50.2 ± 9	51.4 ± 9.7	NA
Gender (Male/Female)	18/32	20/30	NA
BMI (kg/m^2)	21.5 ± 3.5	29.6 ± 3.9	<0.01**
Waist circumference (cm)	92.5 ± 10.3	104 ± 9.5	<0.01**

Results expressed as mean±SD; NA= Not applicable; * *Strongly significant; *Statistically significant.

Table 2: Comparison of lipid profiles of cases and controls studied.

Lipid profile	Cases	Controls	'p' value
Total Cholesterol (mg/dl)	169.56±53.41	148.66±45.17	0.037*
Triglycerides(mg/dl)	171.08±94.23	118.58±50.69	<0.01**
HDL -C(mg/dl)	28.44±10.38	37.08±11.19	<0.01**
VLDL (mg/dl)	34.22±18.85	23.72±10.14	<0.01**
LDL (mg/dl)	106.90±51.96	87.86±36.17	0.036*
NON-HDL	126.7±52.79	114.84±38	0.2
Triglycerides/HDL –C ratio	6.21±3.92	3.65±3.26	<0.01**

Results expressed as mean±SD; ** Strongly significant; *Statistically significant.

Table 3: Comparison of cardio metabolic risk factors in men with metabolic syndrome and controls.

	Controls (n=15)	Metabolic syndrome (n=20)	'p' value
Age (years)	51.06±9.23	50.45±10.34	0.93
Total Cholesterol (mg/dl)	143.27±42.66	155.45±61.57	0.657
Triglycerides(mg/dl)	133.47±72.19	187.9±107.16	0.051
HDL-C (mg/dl)	31.93±9.23	28.45±9.89	0.263
LDL (mg/dl)	84.64±29.48	97.13±54.69	0.828
NON-HDL-C	111.33±37.02	127±59.71	0.777
Triglycerides/HDL –C ratio	4.3±2.36	7.27±4.67	<0.05*

Results expressed as mean±SD; ** Strongly significant; *Statistically significant

Table 4: Comparison of cardio metabolic risk factors in women with metabolic syndrome and controls.

	Controls (n=35)	Metabolic syndrome (n=30)	'p' value
Age (years)	48.6±9.44	51.26±10.11	0.429
Total Cholesterol (mg/dl)	155.63±45.67	157.7±54.6	0.772
Triglycerides(mg/dl)	116.2±84.04	159.87±84.56	<0.01**
HDL-C (mg/dl)	39.28±11.33	31.2±9.11	<0.01**
LDL (mg/dl)	94.2±34.53	96.75±46.33	0.804
NON-HDL-C	116.34±38.85	126.5±48.71	0.357
Triglycerides/HDL-C ratio	3.37±3.56	5.5±3.22	<0.01**

Results expressed as mean±SD; ** Strongly significant; *Statistically significant

Table IV represents the cardiometabolic risk factors in women with metabolic syndrome and controls by Mann Whitney 'U' test. In this study women participants with metabolic syndrome were 30 and controls were 35 in number.

Compared to males who were enrolled, prevalence of metabolic syndrome was more in women and also female participants showed highly significant increase in TG, HDL and TG: HDL ratio compared their controls with p< 0.01. Other parameters like TC, LDL and non HDL showed a moderate significance. These results suggests that the derangement in the lipid ratios is more evident in women than men, that would imply that the exceeding sum of components of metabolic syndrome posed an increased risk than which is incurred by each alone.

The odds ratios for the extent of derangement in lipid ratio TGL: HDL in metabolic syndrome was as follows. In men with TG: HDL-C ratio >3.5 was associated with increased risk of metabolic syndrome, odds ratio=4.9583, 95% CI (1.0088-24.3711), p=0.004 and in women the cutoff of >2.5 showed elevated risk of metabolic syndrome, OR=6, 95% CI (1.5225 to 23.6401) p=0.006.

DISCUSSION

In this study, subjects with metabolic syndrome were selected according to NCEP ATP III criteria. In both cases and controls the anthropometric measures of body mass index (BMI) and waist circumference (WC) were noted with concurrent assay of lipid profile comprising of both estimated and calculated parameters (LDL-C, Non-HDL-C and TG: HDL-C ratio).

There was a statistically significant increase in BMI and WC in metabolic syndrome cases than controls. This ascertains the risk of increased insulin resistance in obese individuals and more so in individuals with central obesity as evidenced from similar studies .[7,8]

The components of metabolic syndrome are individually connected with increased risk for all-cause mortality, mostly cardiovascular disease. However, this study evaluated TG: HDL-C ratio and non-HDL-C in the context of incident cardiometabolic risk prediction. Among the lipid profile parameters, there was a strong association between increased total cholesterol, LDL-C and decreased HDL-C with cardiometabolic risk which is on par with the findings of Avins AL et al, who observed that atherogenic dyslipidemia evinced diabetes mellitus and cardiovascular risk.[9]

Flowers et al, demonstrated that the determination of TG: HDL-C ratio in Indian population can be a useful tool to predict clinical outcomes in apparently healthy individuals who are at increased risk of developing type 2 diabetes mellitus and cardiovascular disease in the background of metabolic syndrome.[10] There was a female preponderance observed and this could be due to the variations in body fat distribution, adipocytes size and the influence of hormones, especially estrogen. The average age of females was 51.26±10.11 year suggesting the emergence of metabolic syndrome post menopause. This finding is consistent with the observations made by Park et al, and adds to the knowledge database of acceleration of cardiovascular disease in postmenopausal women accounting for the temporal separation of incident CVD risk between men and women.[11,12]

Triglycerides and TG: HDL-C ratio was significantly elevated in metabolic syndrome than controls. TG: HDL-C ratio is not only a strong independent predictor of myocardial infarction but also the also the extent of coronary disease. In a study conducted by Da Luz PL et al, TG: HDL-C ratio showed the strongest association with extent of coronary disease scored by Friesinger index.[13] Shou P et al demonstrated in Chinese population that TG: HDL-C was the best predictor of metabolic syndrome in women whereas in men waist-hip ratio was the best predictor.[14]

Even though the non-HDL-C level was elevated in metabolic syndrome patients than in controls, this difference was not statistically significant. Non-HDL-C represents the atherogenic lipoproteins IDL, VLDL, Lp(a), LDL and is recommended by NCEP ATP III guidelines as secondary target for cardiovascular risk. In a study by Li C et al, it was observed that non-HDL-C concentration was strongly associated with metabolic syndrome in American youth.[15]

In the Hoorn study, a large cohort study it was determined that non-HDL-C was a strong predictor of 10 year cardiovascular disease risk incidence in individuals with abnormal glucose homeostasis than in those with normal glucose homeostasis.[16] However, in the current study though the non-HDL-C was elevated in metabolic syndrome individuals it was not statistically significant.

This study is at par with the findings of CARITALY study done to compare the performance of non-HDL-C versus TG:HDL-C ratio for prediction of cardiometabolic risk and target organ damage in a large cohort of overweight/obese children which documented that the odds ratio for insulin resistance, high blood pressure, metabolic syndrome, presence of liver steatosis, increased levels of carotid intima media thickness and concentric left ventricular hypertrophy was higher in children with high levels of TG:HDL-C with respect to children with high levels of non-HDL-C. [17]

CONCLUSION

This study demonstrated that TG: HDL-C ratio and non HDL-C are strongly associated with metabolic syndrome in urban population. In comparison, TG: HDL-C is a better predictor of metabolic syndrome than non-HDL-C. The focus for healthcare professionals should be on identifying individuals with elevated TG: HDL-C and

non-HDL-C, early sub group intervention in metabolic syndrome to prevent cardiovascular disease.

Emergence of metabolic syndrome in post-menopausal women reflects the role of hormones in pathogenesis of metabolic syndrome. However, there is further scope for evaluation of estrogen in conjunction with central obesity in women as cumulative risk for cardiovascular disease. TG: HDL-C and non-HDL-C are simple, cost effective tools for predicting cardiometabolic risk when compared to newer markers and superior to existing conventional markers.

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