SPECTRUM OF LIPID AND LIPOPROTEIN INDICES IN HUMAN SUBJECTS WITH INSULIN RESISTANCE SYNDROME

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Background: Insulin resistance syndrome or metabolic syndrome is one of the major metabolic threats our recently urbanized society is going to face in near future. The management of this syndrome requires a very effective biochemical marker for screening. The objective of this cross sectional study were **t**o compare various lipid and lipoprotein indices in human subjects with insulin resistance syndrome This study was carried out between April 2004 to January 2006 at the department of chemical pathology and endocrinology, Armed Forces Institute of Pathology, Rawalpindi. **Methods:** A total of forty-seven subjects with metabolic syndrome were selected as per the criteria of National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) from a target population diagnosed to have impaired glucose regulation at AFIP. Forty-seven age and sex-matched healthy controls were also included in the study. Insulin resistance was calculated by the method of HOMA-IR, using the formula of Mathew's *et al*. The various lipid and lipoproteins, their ratios and log-transformed versions were evaluated for differences between subjects with metabolic syndrome and controls. Finally the diagnostic performances of these candidate lipid markers were evaluated. **Results:** Results between subjects with metabolic syndrome and controls were found to be significant for serum triglyceride ($p<0.05$), HDL-C ($p<0.05$), triglyceride/HDL-C ($p<0.01$), Log triglyceride/HDL-C ($p<0.01$), total cholesterol/HDL-C ($p<0.01$), LDL-C/HDL-C ($p<0.01$). However there was weak correlation between these lipid based markers and HOMA-IR [(serum triglyceride: r= 0.225), (HDL-C: r= -0.235), (triglyceride/HDL-C: r= 0.333), (total cholesterol/HDL-C: r= 0.239)]. The AUCs for the diagnosis of metabolic syndrome remained highest for HOMA-IR [0.727 (95%CI: 0.642–0.812)], followed by triglyceride/HDL-C [0.669 (95%CI: 0.572–0.766)] and LDL-C/HDL-C [0.639 (95%CI: 0.537–0.742)]. **Conclusion:** The differences for lipids and lipoproteins between subjects with metabolic syndrome and controls remained significant. However, these markers have shown poor correlations with HOMA-IR along-with weaker diagnostic accuracy for the diagnosis of metabolic syndrome. Recommended cut-offs must be used, once these markers are employed in the diagnosis of metabolic syndrome.

Keywords: Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), metabolic syndrome, National Cholesterol Education Program Adult Treatment Panel III (NCEP, ATP III), area under the curve (AUC), impaired glucose regulation (IGR)

INTRODUCTION

Insulin resistance syndrome also known as 'Metabolic syndrome' is characterized by a spectrum of biochemical and clinical abnormalities like hypertension, dyslipidemia, hyperglycemia and obesity.[1,2] The significance of this concept remains in the fact that resistance to insulin action has also been established as a strong predictor of forthcoming cardiovascular and atherosclerotic related complications in different studies.[3] Various organizations like World Health Organization (WHO), National Cholesterol Education Program, Adult treatment Panel III (NCEP,ATP III), European Group for study of Insulin Resistance(EGIR) and American Association for Clinical Pathologist (AACP) have evaluated these connections and formulated detailed guidelines to diagnose and treat subjects with metabolic syndrome.[4–7] However, there are many differences among these diagnostic criteria, which will become more serious once their practical implementation will face regional and local factors.[8, 9] Various direct and indirect methods for demonstrating insulin resistance have been proposed as markers for insulin resistance syndrome; these methods range from mathematical models like HOMA index and Quantitative Insulin Check Index (QUICKI) to technically difficult and mostly experimental methods such as hyperinsulinemic euglycemic clamp test, and Frequently Sampled Intra-Venous Glucose Tolerance Test (FSIVGTT).[10,11]

A country like Pakistan on one hand with meagre laboratory resources may not be able to afford any of these markers; while the ever increasing incidence of coronary artery diseases and stroke in our rapidly urbanizing society further burdens our economy. Insulin resistance syndrome may be an important, if not the most important player in the etiopathogenesis of these atherosclerosis related diseases.[3,12] The lipid and lipoprotein markers, their ratios and log – transformed versions are technically very simple, and can be performed in any peripheral laboratory set up with minimal cost and technical expertise.[13–15] Moreover these markers are already in

clinical application and clinical familiarity will not be a problem.[16] These aspects tempt researchers to evaluate and recommend them as possible candidate markers in the evaluation of metabolic syndrome.

With this background, a research project was planned to compare various lipid and lipoprotein based indices (Total cholesterol, serum triglyceride, HDL-C, LDL-C, triglyceride/HDL-C ratio, log triglyceride/HDL-C ratio, total cholesterol/HDL-C ratio, LDL-C/HDL-C ratio) among subjects with NCEP, ATP III defined metabolic syndrome and healthy age and sex matched controls. Next objective was to correlate these indices with HOMA-IR to evaluate them as a measure of insulin resistance. Lastly the diagnostic performance characteristics of the markers that showed statistically significant correlations were evaluated along with HOMA-IR in the diagnosis of metabolic syndrome.

MATERIALS AND METHODS

This cross-sectional study was conducted at the department of chemical pathology and endocrinology, Armed Forces Institute of Pathology from April 2004 to January 2006.

A total of 5344 subjects presented for evaluation of plasma glucose fasting from September 2004 to August 2005. Among these, 673 individuals were labelled to have impaired glucose regulation. These subjects were requested to volunteer for further evaluation; however 304 subjects gave consent for the study. After further clinical evaluation, the subjects already suffering from diabetes mellitus, hypertension, chronic disorders, and on medications for various reasons were excluded from the study.

Subjects who reported at AFIP for biochemical testing because of promotion and related reasons were requested to volunteer for the study to act as controls. Out of these 47, age and sex matched, healthy controls were selected for the study.

These finally selected subjects (n=110) and controls (n=47) were requested to report in medical fasting state on any working day. 10ml of blood was collected and after separation of serum was aliquoted for further analysis. Based upon the results, 3 groups were made:

Group-1: Insulin resistance syndrome or metabolic syndrome: Finally subjects who met NCEP defined metabolic syndrome criteria (n=47) were selected from the initial sample (n=110)[4,5].

Group-2: Impaired glucose regulation-The leftover subjects who could not be categorized as having insulin resistances syndrome as per NCEP criteria. were put into this group. Only first forty-seven were considered for inclusion.

Group-3: Controls- (n=47)

Plasma glucose was analyzed using GOD-PAP method on Selectra-2 auto-analyzer. Serum total cholesterol, triglycerides and HDL-C were analyzed using CHOD-PAP, GPO-PAP, and indirect phosphotungstic acid method respectively. LDL-cholesterol was calculated using Fridewald's formula. All the above methods are in accordance with NCEP, ATP III specifications. Serum insulin was measured using chemiluminescence's technique on Immulite 1000 (DPC, USA).

Calculations: HOMA-IR was calculated by method of Mathew's *et al*[17] as:

$$HOMA-IR = \frac{FastingSerumInsulin \times FastingPlasmaGlucose}{22.5}$$

Various ratios like triglyceride/HDL-C, Log triglyceride/HDL-C, total cholesterol/HDL-C and LDL-C/HDL-C were calculated using MS Excel.

The data were entered into SPSS- version 11. Descriptive statistics in terms of mean and SD/95% CI were calculated for all demographic and biochemical details. In order to know the differences for various lipid and lipoprotein parameters and their respective ratios between the groups, i.e., subjects in Group-1 [metabolic syndrome (n=47)] and Group-3 [controls (n=47)], *t*-test was applied. These lipids related markers were correlated with HOMA-IR using Pearson's correlation among all the studied subjects i.e., group 1 to 3. Area Under the Curve (AUC) for these lipid markers along with HOMA-IR was measured through ROC curve analysis for the diagnosis of metabolic syndrome. The diagnostic performance characteristics in terms of sensitivity, specificity, and predictive values were calculated at different cut-offs for those markers which showed higher AUC.

RESULTS

The age-wise differences between the two groups are also found to be insignificant. Similarly The gender based differences (Metabolic syndrome: Males–29/47, females–18/47 and controls: males–30/47, females–17/47) are shown in Figure-1. Waist circumferences, HOMA-IR were significantly different between the two groups (Table-1). The comparison of various lipid profile parameters and their different ratios revealed significant differences for all parameters except total cholesterol and LDL-Cholesterol (Table-2). Table-3 shows the correlation between various lipid parameters and their ratios with insulin resistance (HOMA-IR). AIP (Log Triglyceride/HDL-C Ratio) and triglyceride/HDL-C show better correlations (r= +0.311 and r= +0.333); while total cholesterol (r= +0.073) and LDL-C/HDL-C (r= +0.101) demonstrated minimal correlations. The Area Under Curves (AUCs) of those lipid-based markers which showed significant

correlation coefficients with HOMA-IR in the diagnosis of metabolic syndrome are shown in Table-4 and Figure-2. The excellent efficiency demonstrated was observed at 75th percentile for HOMA-IR (74.47%) and triglyceride/HDL-C (63.83%). Based upon the studied data, the various cut-offs with their sensitivities, specificities, predictive values and efficiencies are presented in Table-5.

Table-1: Clinical characteristics and HOMA-IR in subjects with and without metabolic syndrome

Parameter	Healthy controls (n=47) Mean±SD (95% CI)	Metabolic syndrome (n=47) Mean±SD (95% CI)	Significance 2-tailed
Age (Years)	43.69±1.33 (41.04-46.27)	46.13±1.15 (43.84-48.42)	NS
Waist Circumference (cm)	90.38±1.29 (88.11-92.65)	95.51±1.26 (93.23-97.79)	**< 0.05***
HOMA-IR	1.534±0.13 (1.28-1.78)	2.671±0.17 (2.34-3.00)	**< 0.001***
Insulin (mIU/L)	7.127±0.53 (6.09-8.16)	8.851±0.49 (7.73-9.69)	< 0.05

*Statistically significant

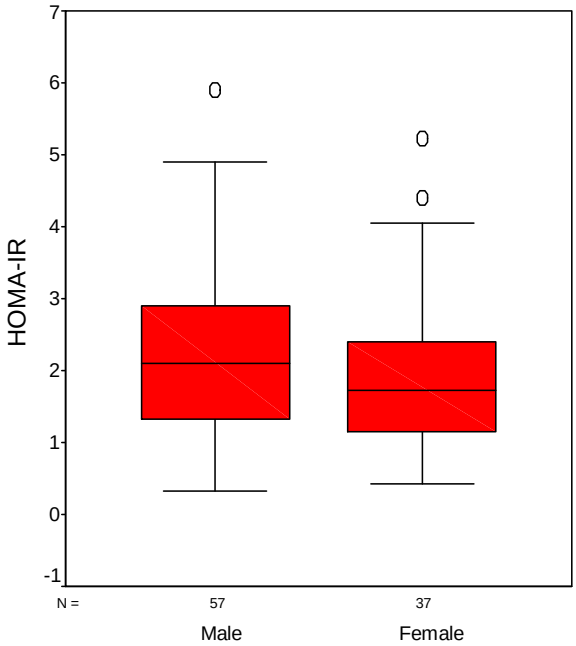

Figure-1: Gender differences for insulin resistance (NS)

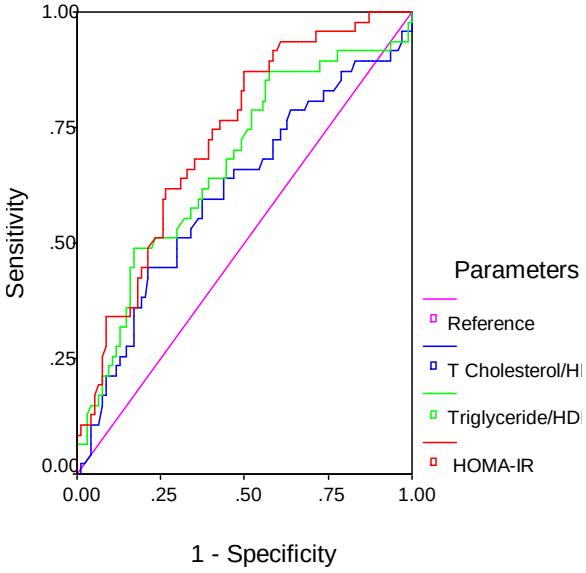

Figure-2: ROC curve analysis showing comparison between important lipid to lipoprotein ratios along with HOMA-IR in the diagnosis of metabolic syndrome

Table-2: Comparison between lipid, lipid to lipoprotein ratios and their log transformed versions between controls and subjects with metabolic syndrome.

Parameter	Healthy controls (n=47) Mean±SD (95% CI)	Metabolic syndrome (n=47) Mean±SD (95% CI)	Significance 2-tailed
Total cholesterol (mmol/L)	4.611±0.10 (4.42-4.80)	4.781±0.11 (4.57–4.99)	NS
Serum triglyceride (mmol/L)	1.612±0.67 (1.44–1.79)	1.901±0.88 (1.74–2.06)	<0.05
HDL-C (mmol/L)	1.1951±0.067 (1.14–1.25)	1.096±0.071 (1.04–1.16)	<0.05
LDL-C (mmol/L)	2.821±0.17 (2.48–2.89)	2.683±0.138 (2.57–3.07)	NS
Triglyceride/HDL-C	1.391±0.09 (1.22–1.57)	1.830±0.10 (1.62–2.04)	<0.01
AIP (Log triglyceride/HDL-C)	0.108±0.029 (0.06–0.16)	0.226±0.031 (0.17–0.28)	<0.01
Total cholesterol/HDL-C	3.969±0.092 (3.69–4.24)	4.546±0.182 (4.16–4.89)	<0.005
LDL-C/HDL-C	2.458±0.38 (1.20–2.72)	2.989±0.21 (2.64–3.34)	<0.05

Table-3: Correlation of various lipid parameters and their ratios with HOMA-IR

		LDL-C/ HDL-C Ratio	Total Cholesterol/ HDL-C Ratio	Total Cholesterol	LDL-C	AIP (Log Triglyceride/ HDL-C Ratio)	Triglyceride/ HDL-C Ratio	HDL-C	Serum triglyceride
HOMA-IR	**Pearson Correlation**	0.101	0.239**	0.073	0.051	0.311**	0.333**	-0.235**	0.225**
	Sig. (2-tailed)	0.235	0.004	0.387	0.548	0.000	0.000	0.005	0.007
	Number	141	141	141	141	141	141	141	141

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

Table-4: Area Under Curve (AUC) for various lipid and lipoprotein ratios in ROC curve analysis.

Test Result Variable(s)	Area Under Curve	95% CI	
		Lower Bound	Upper Bound
HOMA-IR	**0.727**	**0.642**	**0.812**
HDL-Cholesterol	0.414	0.306	0.522
Serum triglycerides	0.661	0.563	0.760
Total cholesterol	0.550	0.444	0.655
LDL- Cholesterol	0.532	0.426	0.638
Triglyceride/HDL-C	**0.669**	**0.572**	**0.766**
AIP (Log Triglyceride/HDL-C)	**0.669**	**0.572**	**0.766**
Total Cholesterol/HDL-C	**0.609**	**0.507**	**0.711**
LDL-C/HDL-C	**0.639**	**0.537**	**0.742**

a. Under the nonparametric assumption. b. Null hypothesis: true area= 0.5

Table-5: Diagnostic performance at important cut-offs for various parameters.

Parameters	Cut-offs	Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Efficiency (%)
HOMA-IR	55	1.47	87.23	55.32	66.13	81.25	71.28
	60	1.70	78.72	59.57	66.07	73.68	69.15
	65	1.81	76.60	65.96	69.23	73.81	71.28
	70	2.03	74.47	70.21	71.43	73.33	72.34
	75	**2.12**	**72.34**	**76.60**	**75.56**	**73.47**	**74.47**
	80	2.24	63.83	85.11	81.08	70.18	74.43
	85	2.93	53.19	89.36	83.33	65.63	71.28
Triglyceride/HDL-C ratio	55	1.36	78.72	48.94	60.66	69.70	63.03
	60	1.42	74.47	51.06	60.34	66.67	62.77
	65	1.52	70.21	55.32	61.11	65	62.77
	70	1.56	63.83	59.57	61.22	62.22	61.70
	75	**1.69**	**61.70**	**65.96**	**64.44**	**63.27**	**63.83**
	80	1.93	53.19	72.34	65.79	60.71	62.77
	85	1.75	44.68	76.60	65.62	58.06	60.64
LDL-C/HDL-C ratio	55	2.33	36.17	51.06	42.5	44.44	43.62
	60	2.65	57.45	59.57	58.70	58.33	58.51
	65	**2.80**	**55.32**	**65.96**	**61.90**	**59.62**	**60.64**
	70	3.01	48.94	70.21	62.16	57.89	59.57
	75	3.06	40.43	76.60	63.33	56.25	58.51
	80	3.21	31.91	80.85	62.5	54.29	56.38
	85	4.29	29.79	85.11	66.67	54.79	57.45

DISCUSSION

The difference between several lipid derived biochemical parameters between metabolic syndrome and age and sex matched healthy controls was found to be significant. The lipid ratios and further their log transformation increments the differences between the two groups. This is in accordance with the conclusions drawn by many previous studies.[18–20] This finding confirms that changes of lipids and lipoproteins in plasma are essential components of metabolic syndrome. The more prevalent of these changes include mild degree of hypertriglyceridemia and slight reduction in the HDL-C.[4,18] However no significant differences have been observed in case of total cholesterol and LDL-C, as highlighted by several studies.[15,21,22] But once the ratios between total cholesterol and LDL-C cholesterol to triglycerides are done, the difference becomes statistically apparent proving the presence of mild degree of dyslipidemias of all lipid and lipoprotein fractions in subjects with metabolic syndrome.[23,24]

Different studies have found variable degrees of correlations between these lipid parameters with measures of insulin resistance.[25,15] Our study has demonstrated weak correlations between these markers and HOMA-IR. Reasons to these differences could be multifold: firstly, dyslipidemias constitute one of the manifestations of insulin resistance syndrome. As per the concept of metabolic syndrome insulin resistance is the basic underlying abnormality, and not dyslipidemias. There are other metabolic abnormalities like impaired glucose regulation, obesity and hypertension, which have their own part to play in the development of metabolic syndrome.[5] The second reason may be the fact that all the cases diagnosed to have these abnormalities included under the umbrella of metabolic syndrome were labelled to have theses problems for the first time, i.e., they were diagnosed relatively early in the process of ongoing atherosclerosis and possibly severe dyslipidemias will surface with progression of disease.[3,26] Lastly racial, regional and social difference in lifestyles

could attribute to these differences, as supported by few of the studies.[24,27,28]

AUC analysis for the candidate lipid to lipoprotein ratios and HOMA-IR indicate weaker performance for the former in the diagnosis of metabolic syndrome. Similar conclusion have been drawn by other studies.[15,16,29] This fact again highlights the importance of measures of insulin resistance, like HOMA-IR in the evaluation and medical decision making for subjects with metabolic syndrome.[3,19] However not all places in an underdeveloped world like Pakistan may be privileged to have facilities for estimation of insulin, so some sort of rough estimate for insulin resistance can be estimated from these lipid to lipoprotein ratios (especially triglyceride to HDL-C ratio). The recommended cut-offs for diagnosis of metabolic syndrome using HOMA-IR, triglyceride/HDL-C ratio and LDL-CLHDL-C are 2.12, 1.69 and 2.80 Laws *et al* have recommended similar cut-offs with sensitivity, specificity and positive predictive values of 64%, 68% and 67%.[16]

The few limitations which could affect the study includes the fact that apart from NCEP, ATP III defined criteria for metabolic syndrome, there are other available definitions for metabolic syndrome as concluded by WHO, EGIR and AACP. So comparison with other criteria may reveal different results. Secondly, the target population mainly constituted an urbanized sample, which may be a confounding factor in the results.

This study may have important clinical implications. There are multiple studies, which have shown the differences for dyslipidemias and their ratios between subjects with and without metabolic syndrome to be significant. However the performance evaluation of these markers may not reveal the same degree of strength for utilizing them as a marker for insulin resistance syndrome. Moreover metabolic syndrome is clustering of multiple metabolic and clinical entities and not just dyslipidemias, and this fact must be considered in the selection of any marker for diagnosis of metabolic syndrome. Finally their inclusion into the workup for diagnosis of metabolic syndrome must only be carried out at appropriate diagnostic cut-offs.

CONCLUSION

The lipid and lipoprotein-based parameters are important components included in the diagnosis of metabolic syndrome. However, these lipid and lipoprotein markers, their ratios and log-transformed forms should not be used markers for the diagnosis of metabolic syndrome. If at all they are incorporated in the diagnostic workup of metabolic syndrome, appropriate cut-offs must be considered.

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