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ORIGINAL ARTICLE

Relationship between Apolipoproteins, Lipoprotein (a) and conventional cholesterol and lipids with insulin resistance.

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ABSTRACT… Objective: To evaluate Apo-A1, Apo-B and Lipoprotein (a) and conventional lipid profile parameters among subjects with high and low insulin resistance groups. **Study Design:** Cross Sectional study. **Setting:** Naval Hospital, Islamabad. **Period:** 2018 to 2020. **Material & Methods:** To include 164 subjects after several exclusions. We carried out conventional lipid indices along with serum insulin, Apo-A1, Apo-B and Lp (a) on these subjects after formal permission. We calculated insulin resistance by using the the HOMAIR index. **Results:** Male population demonstrated higher Apo-B [(Male: 66.44+21.75) vs (Female: 60.84+19.96), p=0.095], triglycerides [(Male: 2.29+1.35) vs (Female: 1.84+0.93), p=0.014] while male showed lower Lp (a) [(Male: 126.13+9.15) vs (Female:16.60+9.39), p=0.095] and Apo-A1. 126.13+21.97) vs (Female: 135.34 +25.24), p=0.017]. Apo-A1 showed highest but still weak positive correlation with HDLc, while Apo-B demonstrated higher positive correlation with total correlation, triglycerides, LDLc, non-HDLc and Lp (a). Among comparison between high and low insulin resistance groups, we could only demonstrate significant differences between triglycerides [Low insulin resistance group: 1.94+1.15 vs High insulin resistance group: 2.41+1.29, p=0.019] and Apo-A1 [Low insulin resistance group: 132.54+23.16 vs High insulin resistance group: 124.91+24.17, p=0.050]. **Conclusion:** Apo-B demonstrated higher positive correlation with total correlation, triglycerides, LDLc, non-HDLc and Lp (a). There were significant differences for triglycerides and Apo-A1 between insulin resistance groups. Female gender and higher insulin resistance groups demonstrated higher Apo-A1 levels.

Key words: Apo-A1, Apo-B, Fasting Triglycerides, HOMAIR, HDL-Cholesterol, Lipoprotein (A), LDL-Cholesterol, Total Cholesterol.

INTRODUCTION

Lipid abnormalities are considered to be associated with insulin resistance and inflammatory responses further leading to coronary artery disease (CAD) and ischemic strokes. The current screening paradigm pivots mainly around traditional lipid profile constituting total cholesterol, triglycerides, Low Density Lipid cholesterol (LDLc) and High Density Lipid Cholesterol (HDLc). Provided their routine use various researchers feel that a conventional lipid profile may not be able to clearly demarcate atherosclerotic cardiovascular disease (ASCVD) risk especially once assessed as 10-year CVD risk.[1] Furthermore, ageing reduce the utility to depict the ability of cholesterol to demonstrate underlying cardiovascular disease (CVD).[2] Apart from this routine patients with normal lipid profile are undergoing primary and secondary angioplasties, which indicate sub optimal risk stratification by traditional lipid markers.

The conventional lipid parameters are now possible supplanted by newer lipid markers like Apolipoproteins and lipoprotein (a) [Lp(a)]. Literature has shown variable result in comparison to conventional lipid indices. Lp(a) has been shown as an independent risk factor in literature to identify underlying cardiovascular disease.[3] However, mixed data prevails in literature for Lp(a) in terms of racial effect on cardiovascular disease where white populace seem to be affected more by this lipoprotein.[4] Data on the utility of new lipid indicators like Apo-A1 and Apo-B have

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been shown in some studies to outperform the conventional lipid indices in earlier studies.[5] Similarly, Kelishadi et al have demonstrated ratio between Apo-B/Apo-A1 to be strongly related with insulin resistance and non-alcoholic fatty liver disease (NAFLD).[6] Contrary to these findings we have data which suggests that Apo-A1 are poorly related with insulin resistance surrogates like Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), Mastuda Index and other risk associations.[7] Similarly, there is evidence that myeloperoxidase modified ApoA1 derived from atherogenic plaques becomes inactivated to perform their role in atherogenic plaques.[8] The association between conventionally defined risks to developments of ASCVD and insulin resistance remains further evaluation.

We therefore planned a study to evaluate the role of Apo-A1, Apo-B and Lip (a) and conventional lipid parameters among subjects with low and high insulin resistance groups.

MATERIAL & METHODS

This study, cross sectional in design was carried out between January-2018 to January-2020 at Naval Hospital Islamabad. Adult hospital visitors either coming for routine medical checkup were requested for inclusion in the study as target population. These potential participants were explained about the type of study and later publication as a research article. Subjects who consented were then interviewed according to a structured questionnaire and were also asked to sign a written consent. Major exclusions included individuals who were having prior history of any long-term medication or acute illness, diagnosed metabolic disease including diabetes, hypertension or ischemic heart disease (IHD) on treatment, pregnancy, were taking any kind of vitamin or other supplementation, autoimmune disorder or had some major surgical procedure in recent past. Initially selected individuals (n=182) were further taken to medical examination room for general physical examination followed by standardized anthropometric examination as per WHO criteria. Few subjects were excluded due to dermatological conditions (n=2) or further refused to be included in study (n=5).

Following medical examination, 10 ml of blood was collected in Na Flouride and plain gel tubes, for various investigations including Serum insulin, total cholesterol, LDL-cholesterol (LDLc), HDL-cholesterol (HDLc), triglycerides, ApoA1, ApoB and Lp(a). Total cholesterol and triglycerides were analyzed by using CHOD-PAP and GPO-PAP methodology on Selectra-ProM analyzer. HDLc and LDLc were analyzed using direct selective detergent based enzymatic method Selectra-ProM clinical chemistry analyzer.

Few other patients were lost to follow up where we required repetitions due to some technical reasons. Serum Apo-A1, Apo-B and Lp(a) were analyzed on "HumaStar 200" clinical chemistry analyzer. Serum insulin was measured by chemiluminescence technique on Immulite®-1000. Insulin resistance was measured using "Homeostasis Model Assessment for Insulin resistance (HOMAIR)" as per formula by Mathew's et al.[9]

Data was entered into SPSS- version 20. We calculated descriptive statistics for age and gender for using descriptive function. Independent sample t test was used to measure the differences for various lipid parameters and age. Pearson's correlation was used to measure the correlation between various conventional and newer lipid indices with insulin resistance (HOMAIR). Independent t test was utilized to compare the two insulin resistance groups for various lipid indices. General linear model was used to measure the difference between the two groups of insulin resistance as fixed factor and Apo-A1 and Apo-B as variables along with gender.

RESULTS

Mean age among study participants was 43.31+10.31. There were 97 males and 67 females in the data set. The gender based differences between various types of cholesterols and triglycerides are shown in Table-I. Serum triglycerides were higher in male subjects in comparison to females, while Apo-A1 and Lp(a) were lower in male subjects. Apo-A1 showed highest but still weak positive correlation with HDLc, while Apo-B demonstrated higher positive

correlation with total correlation, triglycerides, LDLc, non-HDLc and Lp(a). (Table-II)

Among comparison between high and low insulin resistance groups, we could only demonstrate significant differences between triglycerides and Apo-A1. (Table-III) Analysis for Apo-A1 by keeping it as dependent variable and gender and insulin resistance groups as fixed variables via General Linear Model suggested that female and low insulin resistance groups demonstrated higher Apo-A1 levels. (Figure-1) General Linear Model for Apo-B contrary to Apo-A1 showed higher insulin resistance with Apo-B and male gender, however the data was not statistically significant. (Figure-2)

Parameters	Gender	N	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
Total cholesterol (mmol/L)	M	97	4.63	1.05	0.11	0.228
	F	67	4.46	0.77	0.09	
Serum triglycerides (mmol/L)	M	97	2.29	1.35	0.14	0.014
	F	67	1.84	0.93	0.11	
Low density lipoprotein cholesterol (mmol/L)	M	97	2.82	0.85	0.09	0.275
	F	67	2.96	0.74	0.09	
High density lipoprotein cholesterol (mmol/L)	M	97	0.81	0.24	0.03	0.095
	F	67	0.84	0.23	0.03	
Non-High density lipoprotein cholesterol (mmol/L)	M	97	3.82	0.97	0.10	0.151
	F	67	3.62	0.74	0.09	
Apo-A1 (mg/dl)	M	97	126.13	21.97	2.23	0.017
	F	67	135.34	25.24	3.08	
Apo-B (mg/dl)	M	97	66.44	21.75	2.21	0.095
	F	67	60.84	19.96	2.44	
Lp(a) in mg/dl	M	97	13.23	9.15	0.93	0.024
	F	67	16.60	9.39	1.15	

Table-I. Gender effects on various lipid parameters.

Parameter		Apo-A1	Apo-B	Lp(a)	HOMA-IR
Total cholesterol (mmol/L)	Pearson Correlation	0.042	0.439**	0.051	0.113
	Sig. (2-tailed)	0.584	<0.001	0.510	0.144
	N	164	164	164	164
Serum triglycerides (mmol/L)	Pearson Correlation	-0.026	0.308**	-0.015	0.136
	Sig. (2-tailed)	0.733	<0.001	.850	0.078
	N	164	164	164	164
Low density lipoprotein cholesterol (mmol/L)	Pearson Correlation	-0.013	0.308**	.138	0.107
	Sig. (2-tailed)	0.866	<0.001	.074	0.166
	N	164	164	164	164
High density lipoprotein cholesterol (mmol/L)	Pearson Correlation	0.203**	0.106	-.087	0.163*
	Sig. (2-tailed)	0.008	0.168	.263	0.034
	N	164	164	164	164
Non-High density lipoprotein cholesterol (mmol/L)	Pearson Correlation	-0.007	0.445**	.077	0.079
	Sig. (2-tailed)	0.933	<0.001	.320	0.304
	N	164	164	164	164
Apo-A1 (mg/dl)	Pearson Correlation	1	0.084	-.080	0.078
	Sig. (2-tailed)		0.279	.299	0.315
	N	164	164	164	164
Apo-B (mg/dl)	Pearson Correlation	.084	1	-.202	0.125
	Sig. (2-tailed)	.279		.008	0.105
	N	164	164	164	164
Lp(a) in mg/dl	Pearson Correlation	-0.080	-0.202**	1	-0.028
	Sig. (2-tailed)	0.299	0.008		0.714
	N	164	164	164	164

Table-II. Correlation among lipid parameters with insulin resistance.

Parameters	Groups based upon insulin resistance	N	Mean	Std. Dev	Std. Error Mean	Sig. (2-tailed)
Total cholesterol (mmol/L)	Low insulin resistance group	107	4.58	0.88	0.085	0.695
	High insulin resistance group	57	4.52	1.07	0.142	
Serum triglycerides (mmol/L)	Low insulin resistance group	107	1.94	1.15	0.111	0.019
	High insulin resistance group	57	2.41	1.29	0.171	
Low density lipoprotein cholesterol (mmol/L)	Low insulin resistance group	107	2.89	0.74	0.071	0.744
	High insulin resistance group	57	2.85	0.92	0.122	
High density lipoprotein cholesterol (mmol/L)	Low insulin resistance group	107	0.84	0.22	0.021	0.349
	High insulin resistance group	57	0.80	0.26	0.034	
Non-High density lipoprotein cholesterol (mmol/L)	Low insulin resistance group	107	3.75	0.83	0.080	0.864
	High insulin resistance group	57	3.72	0.99	0.131	
Apo-A1 (mg/dl)	Low insulin resistance group	107	132.54	23.16	2.238	0.050
	High insulin resistance group	57	124.91	24.17	3.201	
Apo-B (mg/dl)	Low insulin resistance group	107	62.79	19.31	1.867	0.258
	High insulin resistance group	57	66.72	24.22	3.208	
Lp-a (mg/dl)	Low insulin resistance group	107	15.28	9.53	0.921	0.206
	High insulin resistance group	57	13.33	9.01	1.193	

Table-III. Relationship between conventional and non-conventional lipid parameters within insulin resistance group.

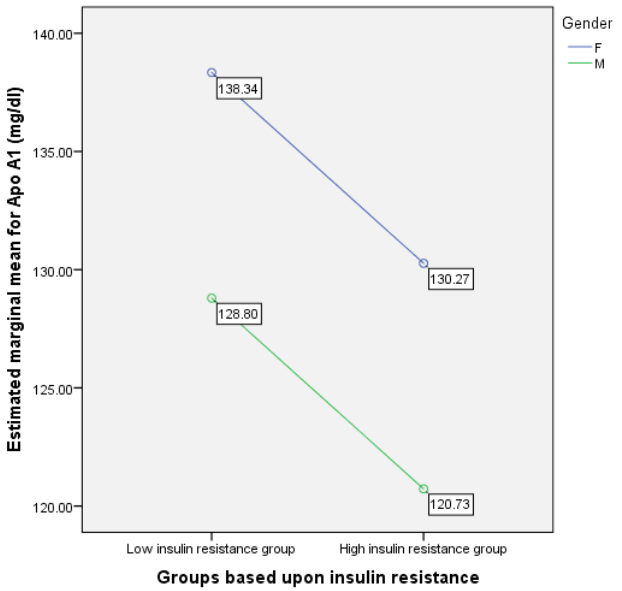

Figure-1. General linear model (GLM) showing the Apo-A1 as variable with gender as a covariate and insulin resistance as a fixed variable. (Model significance=0.05)

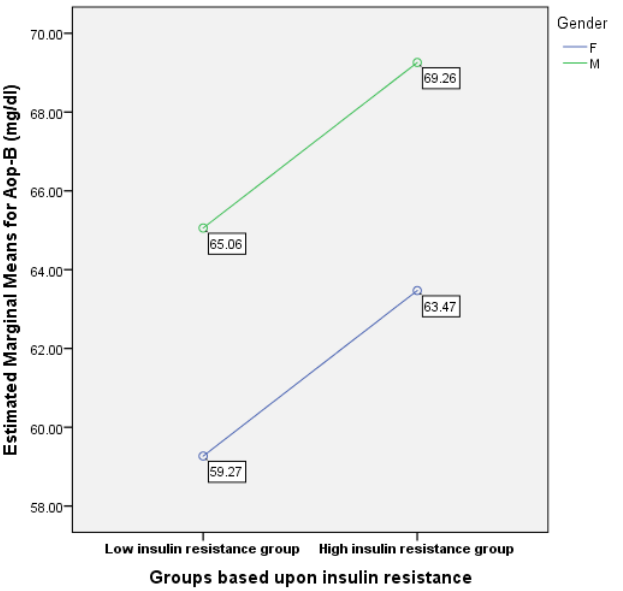

Figure-2. General Linear Model (GLM) showing the Apo-B as variable with gender as a covariate and insulin resistance as a fixed variable (Model significance=0.119)

DISCUSSION

The principal findings from our study included the difference between higher and lower insulin resistance groups was only significant for serum triglycerides and Apo-A1 in comparison to other conventional lipid markers and Lp (a) and Apo-B. In this regard most available data shows similar findings as Feng et al have shown an inverse relationship between insulin resistance and impaired glucose tolerance and Apo-A1.[10] This aspects highlights the protective role of this apolipoprotein in line with HDLc, which has been well-documented overtime for its atherogenic and anti-inflammatory role which contrasts our results.[11] However, not all data supports our

findings as Retnakaran et al have shown that Apo-A1 though associated with HDL C have not been shown to be associated with HOMAIR or other measures of insulin resistance.[12] However, this study, undeniably significant, was conducted among pregnant subjects unlike ours where possibly other factors could be at play. Furthermore, insulin resistance is a multi-faceted disorder with probable contributions from multiple pathogenic triggers.[13] The proof of concept slowly emerging in recent times where recombinant Apo-A1 administration has allowed rapid plasma glucose disposal in tissues.[14] Adding further to support our evidence Huang et al have described the role of dysfunctional Apo-A1 as significant in development of atheromatous plaques.[15]

Contrary to the inverse association between Apo-A1 and insulin resistance, Apo-B and Lp(a) did not show significant with insulin resistance or Apo-A1. However, Apo-B did show modest correlation with total cholesterol and LDL. There could be possible reasons to these findings: Firstly, we do learn that insulin resistance did cause an increase in Apo-B levels in our study, which was not found to be statistically significant probably due to type-II statistical error. Secondly, the average age among our data set is 43 years where probably the process of insulin resistance has not deeply rooted and thus insulin was mostly active and was able to dispose of atherogenic apolipoproteins perhaps earlier as a compensatory response. This phenomena is presented by Weir et al where early stage beta cell defect is marked by hyperinsulinemia to dispose glucose.[16,17]

Our data also highlighted that gender differences were shown to be important for Apo-A1, Apo-B1 and Lp(a), which could confound a generalization based data interpretation especially for Apolipoproteins. Some of the studies have shown separate reference ranges for Apo-A1 and Apo-B with former on the lower side in males and later being on the higher side among males.[18,19] Interestingly Lp(a) levels were not found to be associated with insulin resistance, which looked quite intriguing at first instance. Review of existing data however, supplanted our findings. Fatty liver disease, considered usually a sequel to insulin resistance was observed to have very low Lp(a) indicating an opposite association between insulin resistance and Lp(a).[20] Similarly, Rhee et al have demonstrated that subject with low Lp(a) at baseline were prone to have type-2 diabetes mellitus and higher HOMAIR results further validating our inverse relation between insulin resistance and Lp(a).[21] Moreover, our findings are in accordance with the earlier identified observation about Lp(a) as an independent risk factor for Cardio Vascular Disease (CVD).[22]

Our study had few limitations: This study is a small-sample sized cross-sectional study with more emphasis on lipids, lipoproteins and apolipoprotein evaluation with regards to insulin resistance. A well-controlled trial to fine-tune the exactness of relationship between various measures of insulin resistance and these lipid parameters on a larger sample size must be conducted. Furthermore, we never intended to include known cases of metabolic diseases including ischemic heart disease (IHD), diabetes mellitus and hypertension in our sample size but will be very interesting to learn about changes in Apo-A1. Apo-B and Lp(a) in these diseases.

Though limitations we feel our study has important clinical implications: The study highlights apart from the link of Apo-A1, Apo-B and Lp(a) in comparison with conventional lipid indices in subjects with high and low insulin resistance in our population. Secondly, it identified the requirement of separate reference ranges for both genders, which we feel must be done for their appropriate utilization in clinical care pathways. Lastly, we still need to extend our research to other lipoproteins and enzymes which are involved in transfer of cholesterol between lipoproteins to define personalized medicine for patients.

CONCLUSION

Apo-A1 showed highest but still weak positive correlation with HDLc, while Apo-B demonstrated higher positive correlation with total correlation, triglycerides, LDLc, non-HDLc and Lp(a). There were significant differences for triglycerides and Apo-A1 between insulin resistance groups.

Female gender and higher insulin resistance groups demonstrated higher Apo-A1 levels.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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1	Sikandar Hayat Khan	Corresponding Author, Idear, Sampling lab testing, Statistical data analysis, Medical Writing, Discussion and conclusion.	
2	Ahmed Hayat Afzal	Data compilation, analysis and manuscript finalization.	
3	Rahat Shahid	Data analysis, Medical writing, Manuscript finalization.	
4	Robina Manzoor	Sampling statistical and data analysis.	