

Association of Biomarkers in Metabolic Diseases: Early Prediction of Risk Factors for Cardiovascular Diseases Risk

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ABSTRACT

Background: Depending on the mode of presentation, CVD increases death rates by three to seven times. Serum total cholesterol is a strong predictor of the risk of CV events in people with diabetes. Mortality and morbidity are significantly increased with duration. It is crucial to evaluate the significant risk factors in diabetes.

Methodology: It is a cross-sectional study and comprised of 140 subjects. Demographic details and Blood samples for biochemical parameters of the subjects were collected and recorded. Participants who met the inclusion criteria were divided in to three groups and evaluated the cardiovascular risk markers such as, RDW, TLC, NLR, HsCRP and GGT in metabolic diseases patients,

Results: Group A subjects have shown significant ($p < 0.005$, $p < 0.003$) and positive correlation with NLR. In group B it was found that TLC was statistically significant and positive correlation with DBP. In Group C Subjects with T2DM, obesity, Hypertension and Dyslipidemia, TLC has shown significance ($p < 0.024$) and inverse correlation with SBP and NLR was found to be statistically significant ($p < 0.042$) and inversely correlated with HbA1C.

Discussion: In our study, it was established that one of the metabolic components in all subdivided groups shows significance and positive correlation with TLC and NLR. T2DM subjects have shown significant ($p < 0.005$, $p < 0.003$) and positive correlation with NLR. Subjects with T2DM, obesity, Hypertension and Dyslipidemia, TLC has shown significance ($p < 0.024$) and inverse correlation with SBP and NLR was found to be statistically significant ($p < 0.042$) and inversely correlated with HbA1C.

Conclusion: Thus, knowing the principle of Metabolic diseases not only provides a practical and effective technique to identify individuals with multiple risk factors for cardiovascular diseases, but also provides insight to public health policy planners for future prevention and promotion of healthy living. Finally, patients with metabolic diseases need to face financial strain and it becomes the burden for the developing society.

Key words: Metabolic diseases. cardio vascular diseases, Biomarkers

INTRODUCTION

The pathophysiology of metabolic syndrome is complex and it involves several complex mechanisms. Visceral adiposity has been shown to be an important trigger that activates most of the pathways of MetS (Metabolic syndrome) and it leads to insulin resistance, dyslipidemia, inflammation and endothelial dysfunction. Insulin resistance is a key component of MetS and it is believed to be caused by a combination of genetic and environmental factors.

Adipose tissue plays an important role in regulating energy homeostasis by storing and releasing lipids as needed. Excessive nutrient intake leads to an increase in adipocyte size (hypertrophy) and number (hyperplasia), which can result in reduced blood supply and hypoxia to the tissue. Hypoxia triggers a cascade of events, including adipocyte necrosis and macrophage infiltration, leading to the production of proinflammatory cytokines and adipocytokines such as TNF α , IL-6 and CRP. These adipocytokines contribute to the development of chronic low-grade inflammation in adipose tissue which leads to the development of obesity-related comorbidities such as cardiovascular disease and certain cancers. Impaired storage and release of lipids, exacerbates the development of metabolic dysfunction [1,2]. Endothelial dysfunction is a common complication of insulin resistance, characterized by impaired endothelium-dependent vasodilation and increased vascular tone. Insulin resistance impairs the PI3K pathway, leading to reduced production of Nitric Oxide (NO) in endothelial cells, which is a key mediator of vasodilation. The reduced NO production results in increased vascular tone and impaired blood flow, which predisposes to atherosclerosis [3].

Tasic and Lovic reviewed various Cardio metabolic risk factors. According to the study, the coexistence of T2DM and Hypertension causes a variety of micro and macro vascular diseases in T2DM patients.

In patients suffering from metabolic syndrome, the coexistence of T2DM and Hypertension is very common. In the presence of hypertension, the risk of coronary artery disease and the progression of diabetic complications increases several folds. T2DM and Hypertension comorbidity cases are on the rise all over the world. T2DM and Hypertension have a few risk factors in common, such as Obesity and Dyslipidemia [4,5].

Dyslipidemia is characterized by a range of lipid abnormalities that reflect perturbations in the structure, metabolism and biological activities of both atherogenic (promoting the formation of atherosclerosis) and antiatherogenic (protecting against the formation of atherosclerosis) lipoproteins. Specifically, the dyslipidemia is characterized by elevated levels of lipoproteins containing apolipoprotein B (apoB), elevated triglycerides (TGs), increased levels of small particles of Low-Density Lipoprotein (LDL) and low levels of High-Density Lipoprotein Cholesterol (HDL-C).

In addition, insulin regulates the activity of lipoprotein lipase, which is responsible for clearing VLDL from the circulation. In insulin resistance, there is both an increase in VLDL production and a decrease in VLDL clearance, leading to Hypertriglyceridemia [6].

Elevated levels of pro-inflammatory substances such as HsCRP and interleukins, can accelerate the development of atherosclerosis from the initial chemotaxis of leukocytes in the arterial wall to the rupture of the plaque. This underscores the importance of managing metabolic syndrome and its associated risk factors to prevent the development and progression of cardio vascular diseases [7].

Research study was conducted with 1267 patients to investigate the relationship between degree of obesity and Metabolic Syndrome, inflammatory biomarkers such as Total Leukocyte Count, NL Ratio and

HsCRP were studied. The findings of this study suggest that patients with Obesity and Metabolic diseases, biomarkers were more effective for assessing inflammation and related health risks in study subjects [8].

A simple but important criterion is the width of Red Blood Cell distribution (RDW). Hematology analyzers are devices that measure the size range of red blood cells. Diabetes is a substantial cause of Heart Failure (HF) and it is connected with increased HbA1c levels. RDW has been used to identify anemia and recently it was revealed that RDW can be used to predict the morbidity-to-mortality ratio in chronic heart failure patients. Increased RDW slows the recovery of coronary artery disease, heart failure, stroke and myocardial infarction. RDW elevations cause serious abnormalities in people suffering from acute coronary syndrome [9].

White Blood Cell (WBC) count is a potential marker of acute infection, inflammatory conditions and tissue damage. An increase in the WBC count is closely related with advanced atherosclerosis and the incidence and mortality rate of CVD [10]. In cross-sectional study conducted by Vitool et al. found that the WBC counts are correlated with isolated variables of Metabolic diseases [11].

Neutrophil Lymphocyte Ratio (NLR) is a systemic inflammatory marker linked to mortality and cardiac disorders like CAD and heart failure. NLR is mediated by two different markers: neutrophils (active nonspecific inflammatory mediators) and lymphocytes (inflammatory regulators). A high amount of neutrophils in the blood indicates acute inflammation, whereas a low level of lymphocytes indicates physiological stress. NLR is gaining traction as a promising novel inflammatory biomarker. Inflammation is a major concern among the elderly and is thought to be a natural part of the ageing process. NLR is considered the most cost-effective biomarker and calculating it only requires a complete blood cell count [12].

Early prediction of biomarkers for cardiovascular diseases risk in subjects with Metabolic diseases may prevent the future cardiovascular diseases. In our study, we planned to analysis the cardiovascular risk markers such as, RDW, TLC, NLR, HsCRP and GGT in metabolic diseases patients, so that it may paves the way to control and prevent the cardiovascular diseases by evaluating the association between the biomarkers and metabolic diseases.

METHODOLOGY

It is a cross-sectional study and comprised of 140 subjects. Demographic details and Blood samples for biochemical parameters of the subjects were collected and recorded.

The subjects were recruited in the study after obtaining the written informed consent before the participation in the study. Participants were recruited from the outpatient department of General Medicine, Sri Lalithambigai Medical College and Hospital who met the inclusion criteria. Participants were divided into three groups and Table 1 explains the Gender distribution of each group.

Group A - T2DM, HTN and Dyslipidemia

Group B - T2DM, Obese and HTN

Group C- T2DM, Obese, HTN and Dyslipidemia

(T2DM: Type 2 diabetes mellitus, HTN: Hypertension)

5 ml of blood was withdrawn and dispensed into three vials. In EDTA vial for HbA1c measurement and in fluoride oxalate vial for Fasting Blood Glucose, was analyzed by Glucose Oxidase-Peroxidase method for the analysis of Blood Glucose level, blood in a plain vial for lipid profile, Thyroid function test, Renal function test, Liver Enzymes (GGT), HsCRP. After centrifugation of whole blood at 3000 rpm for 5 mins, serum from plain vial, plasma and Red Blood Cells (RBCs) from anticoagulant vials were collected. Separated serum vials stored at -80°C until analyzed (within 2 months). All routine parameters were assayed on same day and recorded in proforma. For unknown Thyroid disorder and Renal disorders of

study participants, Thyroid function test and Renal Function test were done to follow the exclusion criteria.

Thorough clinical examination of all study subjects was carried out. The blood pressure was measured after the individual sat with the back supported at rest for a period of 5 minutes, the feet on the ground and the right forearm supported with the cubital fossa at heart-level. Systolic Blood pressure and Diastolic Blood pressure were measured by Auscultatory method. Sphygmomanometer was used to measure the blood pressure. Minimum of three readings were taken and the mean of both Systolic and Diastolic Blood Pressure were noted.

Body Mass Index (BMI) was determined by measuring body height and weight. Height was measured in centimeters and body weight was estimated in kilograms (kg) with light clothes and bare feet. BMI was calculated by using the formula weight

(kg)/height (meter²). WHO classification was used to grade the BMI of the subjects.

RESULT

Table 1: Gender distribution of the Groups

	Group A	Group B	Group C
Male	18	22	36
Female	19	15	30
Total	37	37	66

Table 2 illustrates the association and correlation with the biomarkers of Group C subjects T2DM, Hypertension and Dyslipidemia. HsCRP showed a positive correlation with FBG and HbA1C. GGT was associated and it has shown negative correlation with HDL (0.420*(p<0.010*)). RDW shows Negative correlation with HbA1C. NLR was found to be significant and positively correlated with FBG and HbA1C.

Table 2: Pearson correlation between Met's components and Cardiovascular biomarkers within the groups (Group A)

Biomarkers	r value	p value	r value	p value	r value	p value
	HsCRP		GGT		RDW	
FBG	0.39**	0.00**	-0.05	0.73	-0.31	0.06
HbA1c	0.40**	0.00**	0.32**	0.05*	-0.44**	0.00*
SBP	0.18	0.12	0.10	0.54	-0.11	0.50
DBP	-0.13	0.31	0.08	0.61	0.16	0.34
HDL	0.07	0.57	-0.42**	0.01**	0.04	0.78
TGL	-0.07	0.51	0.14	0.40	0.06	0.71
	TLC		NLR			
FBG	0.04	0.79	0.45**	0.00*		
HbA1c	-0.18	0.22	0.47**	0.00*		
SBP	-0.18	0.26	0.30	0.06		
DBP	-0.25	0.13	0.35	0.03*		
HDL	0.24	0.14	-0.03	0.84		
TGL	0.23	0.15	-0.01	0.91		

Table 3 elucidates the association and correlation of biomarkers with Group B subjects with T2DM, Obesity and Hypertension. HsCRP achieved a Significant and positive correlation with FBG, HbA1C

and BMI. GGT shows a positive correlation with HbA1C, SBP and DBP. RDW was found to be significant and negatively correlated with FBG and HbA1C. TLC shows negative correlation with DBP.

Table 3: Pearson correlation between Met's components and Cardiovascular biomarkers within the groups (Group B)

Biomarkers	r value	p value	r value	p value
	HsCRP		GGT	
FBG	0.61**	0.00**	0.02	0.90
HbA1c	0.43**	0.00**	0.38*	0.01*
BMI	0.31**	0.00**	0.14	0.38
SBP	0.18	0.12	0.34*	0.03*
DBP	0.02	0.85	0.36*	0.02*
	RDW		TLC	
FBG	-0.37*	0.02*	-0.20	0.21
HbA1c	-0.36*	0.02*	-0.06	0.71
BMI	0.02	0.86	0.08	0.62
SBP	0.02	0.87	-0.00	0.96
DBP	-0.09	0.59	-0.32*	0.04*
	NLR			
FBG	0.03	0.83		
HbA1c	0.06	0.72		
BMI	-0.09	0.57		
SBP	0.04	0.77		
DBP	0.16	0.32		

Table 4 describes the association and correlation with cardiovascular disease biomarkers in Group C with T2DM, Obesity, Hypertension and Dyslipidemia. HsCRP was associated and positively correlated with FBG and HbA1C. GGT achieved association

and positive correlation with FBG, HbA1C, SBP and TGL. RDW shows a Negative Correlation with BMI and SBP whereas it shows positive correlation with DBP. TLC and NLR were negatively correlated with SBP and HbA1C respectively.

Table 4: Pearson correlation between Met's components and Cardiovascular biomarkers within the groups (Group C)

Biomarkers	r value	p value	r value	P value
	HsCRP		GGT	
FBG	0.17*	0.04*	0.42**	0.00**
HbA1c	0.22*	0.00*	0.45**	0.00**
BMI	0.14	0.10	0.02	0.82
SBP	0.05	0.55	0.30*	0.01**
DBP	0.10	0.24	-0.21	0.08
HDL	0.10	0.23	0.10	0.41
TGL	0.04	0.57	0.28**	0.02**
	RDW		TLC	
FBG	-0.12	0.30	0.15	0.22
HbA1c	-0.21	0.07	0.16	0.19
BMI	-0.28*	0.01*	0.05	0.67
SBP	-0.32**	0.00*	-0.27*	0.02*
DBP	0.29**	0.01*	0.19	0.12
HDL	0.08	0.51	-0.01	0.87
TGL	0.08	0.49	0.18	0.14
	NLR			
FBG	-0.14	0.24		
HbA1c	-0.25*	0.04*		
BMI	-0.04	0.73		
SBP	-0.06	0.58		
DBP	0.04	0.73		
HDL	-0.00	0.96		
TGL	0.01	0.89		

*(FBG-Fasting Blood Glucose, HbA1C-Glycated Hemoglobin, BMI-Body Mass Index, SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, HDL-High Density Lipoprotein, TGL-Triglycerides, HsCRP –High sensitive Reactive Protein, GGT- Gamma Glutamyl Transferase, RDW-Red blood cell Distribution Width, TLC- Total Leukocyte Count, NLR-Neutrophil Lymphocyte Ratio)

DISCUSSION

In India, there is an increasing prevalence of Diabetes and other metabolic diseases in both younger and adult population due to various factors, which has a severe adverse impact on socio-economic and healthcare sectors. HsCRP is a potent marker of a future cardiovascular disease which can be used to assess the risk and to initiate early intervention. HsCRP, a classic acute phase reactant, is an important sensitive marker of low-grade inflammation, higher concentrations of HsCRP have been linked to atherosclerosis and CAD [13].

On Pearson correlation analysis, it was found that FBG AND HbA1c was showing significance and positively correlated HsCRP in all subdivided groups of T2DM individuals (Table 2 to 4). Ridker (2016) observed that HsCRP was firmly related to the incidence of cardiovascular events and also HsCRP performed better than LDL-c, indicating that HsCRP may add substantial prognostic information to that conveyed by the Framingham risk score [14].

TLC and its components are typical inflammatory markers that are commonly available and also, it is inexpensive to measure. In our study, it was established that one of the metabolic components in all subdivided groups shows significance and positive correlation with TLC and NLR. T2DM subjects have shown significant ($p<0.005$, $p<0.003$) and positive correlation with NLR (Table 2). In group B (Table 3) it was found that TLC was statistically significant and positive correlation with DBP. In Group C Subjects, TLC has shown significance ($p<0.024$) and inverse correlation with SBP and NLR was found to be statistically significant ($p<0.042$) and inversely correlated with HbA1C (Table 4). In this study also, we established the association between GGT and other components. T2DM subjects with obesity and hypertension have shown an association and positive correlation with GGT ($p<0.035$, $p<0.026$). Table 3 shows both Systolic and Diastolic Blood pressure was strongly

associated and positively correlated with GGT.

Interestingly in this study it was found GGT was found to be associated and positively correlated with FBG, HbA1C, SBP and TGL, $p<0.00$, $p<0.00$, $p<0.13$, $p<0.02$ in Group C Subjects (Table 3). Similarly, in Group A subjects High Density Lipoprotein (HDL) was found to be significant (<0.010) and on Pearson correlation analysis it shows negative correlation with GGT. Reason behind the pathogenesis of NAFLD appears to be insulin resistance which results lipolysis and excess deposition of fat on liver and together causes inflammation, oxidative stress and which in turn leads to the elevated liver enzymes. Free radicals generated in Hyperglycemia consume glutathione which induces the expression of GGT in liver [15]. Group A subjects have shown significant ($p<0.005$, $p<0.003$) and positive correlation with NLR (Table 2). In group B (Table 3) it was found that TLC was statistically significant and positive correlation with DBP. In Group C Subjects with T2DM, obesity, Hypertension and Dyslipidemia, TLC has shown significance ($p<0.024$) and inverse correlation with SBP and NLR was found to be statistically significant ($p<0.042$) and inversely correlated with HbA1C (Table 4).

Lee et al. (2008) has explained the positive correlation and relationship between the GGT and with other markers of inflammation such as HsCRP and TLC among 4562 individuals for the cardiovascular risks (Lee et al. 2008). In a study, conducted by Switonska et al. (2019) includes 58 patients with Ischemic stroke were analyzed and it was HsCRP level greater than 3mg/L also establishes the Higher NLR [16,17]. Similarly, in this study also it was found positive correlation with HsCRP and total TLC count.

CONCLUSION

The rapidly rising metabolic diseases population in India requires Immediate and resourceful measures. Environmental factors have a tremendous influence on

programming vascular complications in metabolic diseases. Thus, knowing the principle of Metabolic diseases not only provides a practical and effective technique to identify individuals with multiple risk factors for cardiovascular diseases, but also provides insight to public health policy planners for future prevention and promotion of healthy living. Finally, patients with metabolic diseases need to face financial strain and it becomes the burden for the developing society.

Declaration

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Conflict of Interest: The authors declare no conflict of interest.

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