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Association of Inflammatory Cytokines with Hemostatic Variables in Ischemic Heart Disease Subjects

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Abstract:
Objective: - *The aim of this study was to find the association of Plasma IL-6 with Fibrinogen and t-PA in IHD subjects (STEMI subjects).*
Materials and Methods*: The study was conducted on 110 STEMI subjects and 110 age and gender matched healthy controls. Plasma IL-6, Fibrinogen and t-PA levels were estimated by ELISA technique. Difference in all the parameters between STEMI subjects and healthy subjects were analyzed by t-test and correlation between two parameters were accessed with Pearson's correlation test.*
Results*: STEMI subjects had significantly high levels of Plasma IL-6, Fibrinogen and t-PA when compared with healthy controls. A positive significant correlation was observed between IL-6 and Fibrinogen while a positive non-significant correlation between IL-6 and t-PA was found in this analysis.*
Conclusion: *We concluded that inflammatory cytokines causes deleterious activities and a negative inotropic impact and induce apoptosis in myocardium exposed to injury. Hemostatic variables have significant etiologic roles in the advancement of cardiovascular occasions. Specifically, estimation of both fibrinogen and t-PA levels may assist with distinguishing those at high danger of future cardiac events.*
Key Word*:* IL-6, t-PA, STEMI, BMI, SBP, DBP

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I. Introduction

Ischemic coronary illness additionally called as coronary illness or coronary artery sickness, utilized for heart issues because of limited coronary flow that supply blood to the heart muscle. It very well might be occour by blood clump or tighting of vein, constantly it is a development of plaque, which is called atherosclerosis.[1] Around 33% deaths caused by cardiovascular illnesses worldwide[2] in which ischemic coronary illness is generally boundless.[3] In 21st centuary this infection became significant danger factor.[4] Numerous individuals live with nondestructive ischemic coronary illness and weakened personal satisfaction.[5] Generally 70% of patients have various danger factors for IHD and 2-7% has no danger factors.[6]

Overall estimated 4.5 million deaths because of cardiovascular infections in non-industrial nations.[7] In 1990, 3.5 million passings of the 6.5 million worldwide passings brought about by ischemia of heart. In 2008 WHO assessed that 17.3 million passings (30% of all worldwide demise) was because of cardiovascular problem. In which 7.3 million passings were because of ischemic coronary illness and in 2016 more than 9.0 million passings were because of ischemic coronary illness. Projections gauge that rough 7.8 million passings represent IHD in 2020.[8]

The primary favorable to inflammatory cytokines have a place with the Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-17 (IL-17), Interferon and tumor necrosis factor (TNF) families. For the commencement of incendiary course interleukin-1 is important[9,10] and cytokines have a place with interleukin-6 family have both immunoregulatory and foundational impacts.[11] The interleukin-17 group of cytokines includes six individuals that are proinflammatory.[12] The three interferon families have antiviral properties[13] and the tumor necrosis family is fundamental for inflammation actuation.[14]

Fibrinogen was delegated a sinewy protein with 340 kDA glycoprotein which needed for hemostasis, wound mending, aggravation, angiogenesis and other body capacities. This is a dispersible macromolecule however when respond with thrombin convert into fibrin which isn't dispersible and enacted by an enzymatic pathway. The fibrin coagulation is important to forestall blood misfortune and wound recuperating. Fibrinogen is additionally essential for hemostasis in which platelet aggragation occour at the site of injury.[15] Numerous explores propose that apoplexy, endothelial brokenness and aggravation are identified with heart sicknesses.

'Northwick Park Heart Study' revealed that expanded degrees of fibrinogen, factor VII, factor VIII and von Willebrand factor (vWf) anticipated future coronary illness.[16]

Debasement of fibrin is reliant upon plasminogen and tissue plasminogen activator (t-PA) restricting by means of trademark collaborations. In t-PA, five primary types are available and different restricting spots are accessible on t-PA for cells and fibrin however for fibrinolysis F and K2 locales are generally significant.[17] It has been proposed that vWF, fibrin, t-PA are related to heart illnesses.[18] These variables are identified with irritation to injury which gives a further pathway among them and heart sicknesses.[19]

Myocardial Infarction is the after effect of coronary course apoplexy and consequently markers of expanded thrombotic inclination may be related with expanded danger of coronary illness (CHD). Attributable to their job in the pathophysiology of platelet collection and fibrin turnover, it has been proposed that von Willebrand factor antigen (vWF), fibrin D-dimer and tissue plasminogen activator antigen (t-PA) are causally identified with CHD hazard.[18] These elements are likewise associated with the incendiary reaction to injury (counting blood vessel injury), which may give a further pathway among them and CHD hazard.[19]

II. Material And Methods

Subjects

The current examination was led on patients of Ischemic Coronary Disease (STEMI) conceded or going to in Department of Cardiology, J.L.N. Medical College, Ajmer. Conclusion of Ischemic Coronary illness was confirmed after assessment of ST section in Electrocardiogram (ECG) by experienced cardiologists. The subjects remembered for the examination were 110 patients experiencing ST segment elevated myocardial infarction. 110 healthy control subjects of same age gathering of either gender were chosen for the examination. Consent from every one of the subjects was taken for the investigation. Perplexing variables which could meddle in the biochemical investigation of study subjects and change the outcomes were taking anti hypertensive medications particularly mitigating drugs, subjects with past history of Ischemic Coronary Illness, subjects on oral anticoagulants, subjects with Kidney and Liver illnesses, patients experiencing Diabetes Mellitus, Malignant growth and Thyroid illness, women on chemical substitution treatment, subjects with some other Immune system illnesses and pregnant ladies etc. were excluded from the study.

Measurements

People who were able to get subject of this examination were told about the pre insightful factors. Venous blood sample was taken by aseptic method and gathered in tubes containing Potassium Ethylene Di-amine Tetra Acidic Acid (2% K2 – EDTA) as anticoagulant for plasma separation. Plasma was isolated by centrifugation at 2500 RPM for 10 minutes. Aliquots of tests were set up by moving them into independent plain vials. These were marked appropriately and put away at – 20oC until measured. Plasma IL-6, Fibrinogen and t-PA were measured by ELISA technique[20] using Biorad ELISA reader.

Data analysis

The results were presented as Mean ± SD for all quantitative parameters. Differences between means of various parameters were compared by independent t-test. Correlations between variables were tested using the Pearson's correlation test. Statistical analysis was considered to be statistically significant at $p < 0.05$.

III. Result

Table -1 shows significantly ($p<0.0001$) high levels of BMI, SBP and DBP was found in STEMI subjects when compared with healthy controls. Plasma IL-6, Fibrinogen and t-PA levels were also found significantly ($p<0.0001$) high in STEMI subjects.

Table no 1: Status of various parameters in STEMI and Control subjects.

Parameter	Healthy Controls (n = 110)	STEMI Subjects (n = 110)	p-value*
Age (yrs)	57.8 ± 11.9	59.2 ± 10.8	>0.05
SBP (mm/Hg)	116 ± 7.35	162 ± 8.03	<0.0001
DBP (mm/Hg)	82.7 ± 7.79	110 ± 3.25	<0.0001
Pulse rate (Count/minute)	70.4 ± 2.63	69.7 ± 2.97	>0.05
Interleukin-6 (pg/ml)	3.77 ± 1.37	10.3 ± 0.53	<0.0001
Plasma Fibrinogen (mg/dL)	278 ± 48.6	530 ± 32.3	<0.0001
Plasma t-PA (ng/mL)	4.4 ± 1.78	10.7 ± 0.51	<0.0001

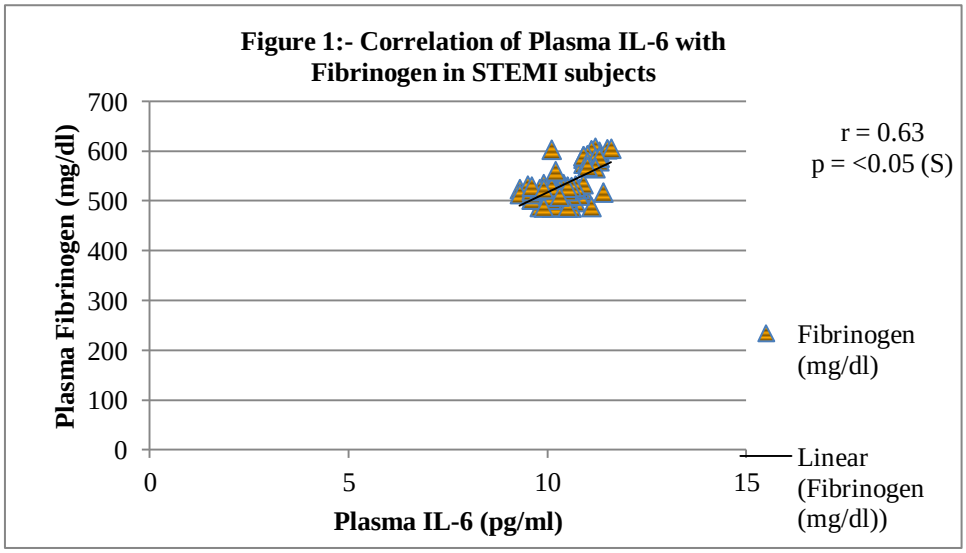
*$p<0.05$ was considered as statistically significant.

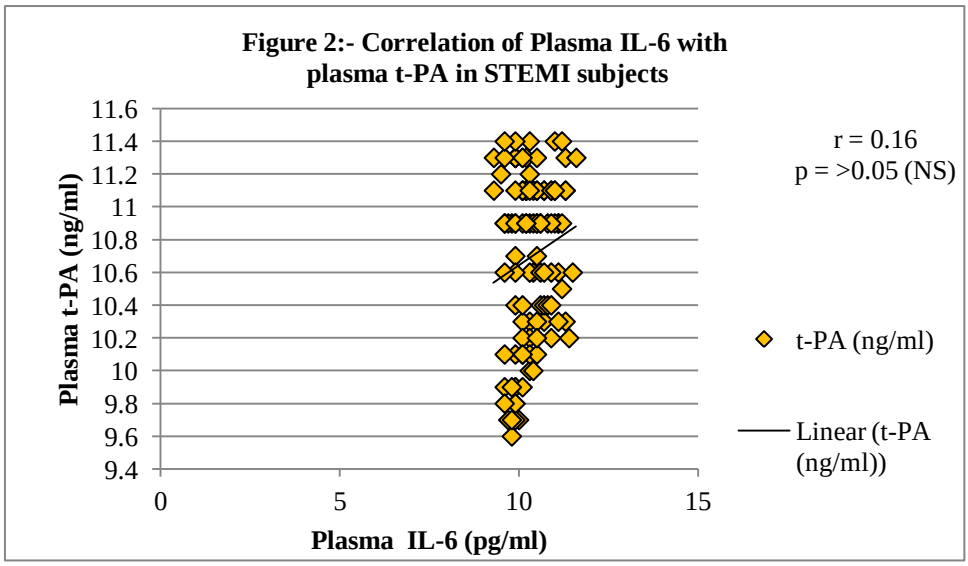
As it is shown in table 2, a significant positive correlation of Plasma IL-6 with plasma fibrinogen and a non-significant positive correlation of Plasma IL-6 with t-PA was found in our study (Figure 1, 2).

Table no2: Correlation of Plasma IL-6 with Plasma Fibrinogen and t-PA in STEMI subjects.

Parameters	r-value	p-value	Significance*
Plasma Fibrinogen (mg/dL)	0.63	<0.0001	HS
Plasma t-PA (ng/mL)	0.16	0.094	NS

*HS=Highly Significant
*NS=Non-Significant





IV. Discussion

IHD is a chronic inflammatory state of the blood vessels. It is a major socioeconomic problem and also a threat of public health throughout the world, since they significantly contribute to the global morbidity. Some common CVDs, including atherosclerosis, vascular disease and heart disease, occupy a strong position in the structure of disability and mortality worldwide.[21,22] Inflammation contributes a significant role in the etiology of myocardial infarction (MI), hypertension, angina pectoris (AP), and ischemic heart disease (IHD) or coronary

artery disease (CAD).[23,24] MI is caused by atheromatous process, since this process blocks coronary artery inhibiting proper blood flow through it.[23] Atherosclerosis is the major cause of IHD. Intima erosion is caused by atherosclerosis, which leads to subsequent ischemia.

Despite the fact that hypertension is a chief danger factor for cardiovascular end focuses, proof in regards to its position in the assessment of patients with ACS has not given clear-cut results. Apparently hyper-tension may act in a cardioprotective manner at times, for example, the intense period of a MI when hypertensive patients seem to have better in-hospital anticipation.[25] The pathophysiological system of pulse rate related mortality is still subtle. It has been shown that in patients with CAD, elevated pulse rate produces coronary vasoconstriction, possibly further hindering oxygen supply.[26]

In the current investigation plasma IL-6, Fibrinogen and t-PA levels were fundamentally higher in STEMI subjects in contrast with control subjects. An exceptionally highly significance ($p=0.0001$) was seen between the groups. An investigation done by Nagendra Boopathy Senguttuvan et al[27] on association of Cytokines IL-6, IL-10, IL-18, TNF-α in Acute Coronary Syndrome and found that Serum IL-6, IL18, and TNF-alpha were fundamentally higher in ACS gatherings (STEMI and NSTEMI) when contrasted with the control group. There was no significant contrast in serum level of IL-10 between STEMI, NSTEMI gathering and controls.

A significant positive relationship of plasma Interleukin-6 with plasma Fibrinogen ($p=0.0001$) was found in STEMI subjects while non critical positive association with plasma t-PA ($p=>0.05$) was found in present appraisals Ioanna Tzoulaki et al[28] uncovered that raised levels of a few inflammatory, hemostatic, and rheological factors were related with future CVD even subsequent to representing customary danger factors and for asymptomatic atherosclerosis as estimated by the ABI. Prominently, IL-6 showed the most noteworthy and most reliable relationship between various examinations and diverse infection signs. Be that as it may, these markers add just unassuming prognostic data to customary danger components and ABI, and they were not explicit to CVD forecast. They found a gradual CVD hazard for individuals with IL-6, t-PA, Lp(a), or ICAM-1 in the top tertile. Additionally, the concurrent change of these 4 markers gave some additional data past that of conventional danger factors for CVD. One potential clarification of this impact could be that these markers may advance atherothrombosis through particular pathways. It should be anxious, notwithstanding, that the utilization of a score dependent on expanded degrees of biomarkers needs cautious thought from a clinical perspective in wording of cost and time adequacy. CRP and fibrinogen have been broadly concentrated in numerous epidemiological investigations corresponding to CVD, which shows both consistency and generalizability.[29] The proinflammatory cytokine IL-6 is less concentrated yet has as of late got consideration as a potential danger factor for CVD on the grounds that it is thought to advance atherosclerotic movement through both inflammatory and hemostatic pathways. [30]

So these markers have additionally been related with proportions of early atherosclerotic disease which may additionally initiate their creation. Their relationship with occurrence of IHD was genuinely critical after change not just for regular IHD hazard factors yet additionally for a proportion of subclinical illness.

V. Conclusion

We concluded that Inflammatory cytokines causes deleterious activities and a negative inotropic impact and induce apoptosis in myocardium exposed to injury. Hemostatic variables have significant etiologic roles in the advancement of cardiovascular occasions. Specifically, estimation of both fibrinogen and t-PA levels may assist with distinguishing those at high danger of future cardiac events. Since our discoveries depend on a generally low number of vascular occasions, further bigger investigations are expected to validate the findings.

References

[1]. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Fihn SD, Fraker TD Jr, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV, Gibbons RJ, Alpert JS, Antman EM, Hiratzka LF, Fuster V, Faxon DP, Gregoratos G, Jacobs AK, Smith SC Jr; American College of Cardiology; American Heart Association Task Force on Practice Guidelines 2002. Committee on the Management of Patients with Chronic Stable Angina.

[2]. Mozaffarian D, Benjamin E, Go A, et al.: Heart disease and stroke statistics-2016 update. A report from the American Heart Association. Circulation. 2016, 133:e38-e46.

[3]. Roth GA, Johnson C, Abajobir A, et al.: Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017, 70:1-25.

[4]. Prabhakaran D, Jeemon P, Sharma M, et al.: The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990-2016. Lancet Glob Health. 2018, 6:1339-1351.

[5]. Moran AE, Forouzanfar MH, Roth GA, et al.: Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. Circulation. 2014, 129:1483-1492.

[6]. Sampasa-Kanyinga H, Lewis RF: Frequent use of social networking sites is associated with poor psychological functioning among children and adolescents. Cyberpsychology Behav Soc Netw. 2015, 18:380-385.

[7]. Okrainec, K., Banerjee, D., & Eisenberg, M. Coronary Artery Disease in the Developing World. American Heart Journal 2004; 148 (1),: 7-15.

[8]. Backer, G. The Global Burden of Coronary Heart Disease. Medicographia 2009; 31 (4): 343-348.

[9]. Narayanan KB, Park HH. Toll/interleukin-1 receptor (TIR) domain-mediated cellular signaling pathways. Apoptosis 2015; 20: 196-209.
[10]. Dinarello CA, van der Meer JW. Treating inflammation by blocking interleukin-1 in humans. Semin Immunol 2013; 25: 469-484.
[11]. Schaper F, Rose-John S. Interleukin-6: Biology, signaling and strategies of blockade. Cytokine Growth Factor Rev 2015.
[12]. Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. Nat Rev Immunol 2013; 13: 397-411.
[13]. Katz MG, He Y, Gale M, Jr. Viruses and interferon: a fight for supremacy. Nat Rev Immunol 2002; 2: 675-87.
[14]. Sedger LM, McDermott MF. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants - past, present and future. Cytokine Growth Factor Rev 2014; 25: 453-472.
[15]. Weisel JW and Rustem I. Litvinov. Fibrin Formation, Structure and Properties. Subcell Biochem. 2017 ; 82: 405–456.
[16]. Meade TW, Mellows S, Brozovic M. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1986; 2(8506):533–537.
[17]. Colin Longstaff,Craig Thelwell,Stella C. Williams,Marta M. C. G. Silva,Laszlo Szabo,and Krasimir Kolev. The interplay between tissue plasminogen activator domains and fibrin structures in the regulation of fibrinolysis: kinetic and microscopic studies. BLOOD, 2011; 117(2): 661-668.
[18]. Lowe GDO & Rumley A. Use of fibrinogen and fibrin D-dimer in prediction of arterial thrombotic events. Thromb Haemost 1999; 82:667–672.
[19]. Libby P. Inflammation in atherosclerosis. Nature. 2002; 420: 868-874.
[20]. Engvall E. Enzyme linked immunosorbent assay. The Journal of Immunology 1972; 109(1): 129-135.
[21]. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm 2010; 53-59.
[22]. Petrukhin IS, Lunina EY. Cardiovascular disease risk factors and mortality in Russia: challenges and barriers. Public Health Rev 2011; 33: 436-442.
[23]. Hansson, GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685–1695.
[24]. Bucova, M, Bernadic, M, Buckingham, T. C-reactive protein, cytokines and inflammation in cardiovascular diseases. Bratisl Lek Listy 2008; 109(8): 333–340.
[25]. Konstantinos K, Costas T, Areti K, Manos M, Alexandros K, Michalis D and Dimitris T. Hypertension and patients with acute coronary syndrome, putting blood pressure levels into perspective. J Clin Hypertens. 2019; 21:1135-1143.
[26]. Sambuceti G, Marzilli M, Marraccini P. Coronary vasoconstriction during myocardial ischemia induced by rises in metabolic demand in patients with coronary artery disease. Circulation 1997;95:2652–2659.
[27]. Nagendra Boopathy Senguttuvan, Arulselvi Subramanian, Garima Agarwal, Sundeep Mishra, V K Bahl. Association of Cytokines IL6, IL10, IL18, TNFα in Acute Coronary Syndrome. J Cardio Vasc Med 2019; 5(205):1-9.
[28]. Ioanna Tzoulaki, Gordon D. Murray, Amanda J. Lee, Ann Rumley, Gordon D.O. Lowe, F. Gerald R. Fowkes. Relative Value of Inflammatory, Hemostatic, and Rheological Factors for Incident Myocardial Infarction and Stroke The Edinburgh Artery Study. Circulation 2007; 2119-2127.
[29]. Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant met-analysis. JAMA. 2005; 294: 1799-1809.
[30]. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2000;101:1767–1772.

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