International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2015): 6.391

Role of Inflammation Biomarkers and Coronary Artery Disease Analyzed According to Coronary Risk Factors

P. Vargu[1], M. Vargu[2], E. Konda[3], M. Lezha[4]

[1]Dermato-Venerology Clinic, Tirana, Albania

[2, 3, 4] Cardilogy Clinic, Tirana, Albania
University Hospital Center "Mother Teresa", Tirana, Albania

Abstract: ***Numerous studies have shown that elevated levels of biomarkers are associated with increased cardiovascular risk. We advocate greater use of CRP and alfa-TNF measurements in clinical practice to identify patients at high risk in a variety of situations.***

Keywords: hs-CRP, Alfa –TNF, inflammation, atherosclerosis, risk factors.

1. Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in the developed world. Lipids have traditionally and solidly been linked to atherogenesis, but only lately has the role of inflammation in atheroma formation been given the attention it deserves. Clinical studies have provided the first evidence implicating inflammation in atherosclerosis1;2.

The experimental studies that followed have established the inflammatory nature of arterial lesions. Much research has been carried out on the diagnostic and clinical value of specific serum or tissue inflammatory biomarkers. Finally, the potential for medical preventative or therapeutic intervention in the inflammatory component of arterial disease is being fervently investigated.

Hs-CRP dosage methods

Nowadays there are being used two CRP dosage types in the lab practice. This derives by the fact that CRP normally exists in plasma in very low concentrations, which are independent by acute infections but can change during cardiovascular diseases that are associated with a low scale chronic inflammation. In cases of large scale acute inflammations developed in trauma, surgery, bacterial infections and arthritis, CRP levels are being measured with the common lab methods because these situations cause a large increment of the CRP concentrations. Usually the acute inflammations are being associated with CRP increment in values higher than 10 mg/L, while on the other hand the low scale chronic inflammation caused by atherosclerosis is being associated with CRP increment in values lower than 10 mg/L. The low grade inflammations and viral infection in general, cause a CRP concentration increment in the range of 10-50 mg/l, while the high grade and active ones, or the bacterial infections cause an increment of 50-200 mg/l.

The standard clinical methods for CRP dosage have a detection limit of 3-8mg/L. Therefore these methods lose its sensitivity in the normal low level and cannot be used in effective way for the prevention of vascular risk. Nowadays, as a conclusion from this fact, there are being developed and used various methods called “high-sensitivity" or "ultra-sensitive", and furthermore there are being placed standardization programs to ensure comparability among hs-CRP dosage methods. So basically today, it is the hs-CRP dosage method covering the 0.1-10mg/L values, the one which provides us a very good estimation of a chronically and latent inflammation.

2. Material and Method

There have been taken into examination a total number of 1033 patients which were analyzed according to: age, gender, HTA presence, Diabetes Melitus presence, level of total Cholesterol and Triglycerides, presence of Acute Coronary Syndrome heritage, as well as inflammation biomarker level in blood where in our case were examined two of them; hs-CRP (high sensitivity C-reactive protein) and TNF-alpha (tumor necrosis factor).

All these individuals underwent a Cathlab examination which provided details about the presence of Acute Coronary Syndrome for single, double or triple vessel. The excluding factor for entering into this study was the age younger than 18 yrs old and the presence of known inflammatory diseases.

To render the statistic analysis there has been made use of these tests: CHI square and ANOVA.

3. Outcomes

3.1 Relation among CRP and TNF-alpha values with single, double and triple vessel blockage

The mean PCR value is significantly higher in triple vessel blockage (11.7), compared to double vessel blockage (8.8.) and to single vessel (7.7) [ANOVA test: **P=0.008**]. Hence, hs-CRP is an independent risk factor at CAD patients and it is associated (related) in linearity with the vessel blockage, i.e. the hs-CRP values are significantly increased with the vessel blockage increment.

This finding is reflected in the below mentioned table:

Table 1: hs-CRP mean value presentation according to vessel blockage at CAD patients

CRP

	N	*Average*	*SD*	*Standard deviation*	*95% Cl of average*		*Minimum*	*Maximum*
					Lower bond	Upper bond		
Single vessel	227	7.6677	11.27657	.74845	6.1929	9.1426	.30	68.30
Double vessel	185	8.8159	13.00958	.95648	6.9288	10.7029	.30	100.00
Triple vessel	214	11.6978	16.86348	1.15276	9.4255	13.9701	.30	100.00
Total	626	9.3847	13.99009	.55916	8.2867	10.4828	.30	100.00

On the other hand, TNF-alpha has an inconsistent relation with vessel blockage: TNF-alpha average is higher at triple vessel CAD block, but there is an incompatibility due to the fact that TNF-alpha is lower at CAD patients with double vessel block compared to single vessel block subjects. (ANOVA test: **P=0.156** i.e. the relation between TNF-alpha and vessel blockage at CAD patients is not statistically significant). This finding is reflected in the below mentioned table

Table 2: TNF-alpha mean values according to vessel blockage in CAD patients

TNF-alpha

	N	Average	SD	Standard deviation	95% Cl of average		Minimum	Maximum
					Lower bond	Upper bond		
Single vessel	223	14.4315	8.57191	.57402	13.3003	15.5627	4.40	86.30
Double vessel	182	12.9742	6.86234	.50867	11.9705	13.9779	4.06	76.60
Triple vessel	212	14.5917	10.98310	.75432	13.1048	16.0787	5.71	141.00
Total	617	14.0567	9.06269	.36485	13.3402	14.7732	4.06	141.00

3.2 Relation between age and vessel blockage at CAD patients

There is a linear positive relation between age and vessel block at CAD patients: average age is significantly higher in function with vessel block (ANOVA test P **<0.001** :

This finding is reflected in the below mentioned table:

Table 3: Relation of age and vessel block in CAD patients

Age

	N	Average	SD	Standard deviation	95% Cl of average		Minimum	Maximum
					Lower bond	Upper bond		
Single vessel	227	58.44	9.939	.660	57.15	59.74.	29	85
Double vessel	186	59.73	9.062	.664	58.42	61.04	31	82
Triple vessel	215	62.52	8.255	.563	61.41	63.63	41	83
Total	628	60.22	9.280	.370	59.49	60.95	29	85

3.3 Relation between gender and vessel blockage at CAD patients

On the other hand, there is no relation between gender and vessel blockage at CAD patients (Fisher's exact test: **P=0.599).**

This finding is reported in the below mentioned table:

Table 4: Relation between gender and vessel blockage in CAD patients

Vessel blockage	Gender		Total
	Males	Females	
Single vessel	183	44	227
	35.50%	39.30%	36.10%
Double vessel	157	29	186
	30.40%	25.90%	29.60%
Triple vessel	176	39	215
	34.10%	34.80%	34.20%
Total	516	112	628
	100.00%	100.00%	100.00%

3.4 Relation among cholesterol and triglycerides with vessel blockage in CAD patients

There's a significant relation of vessel blockage with the cholesterol and triglyceride level in CAD patients: the higher the vessel blockage the higher will be the mean values of cholesterol and triglycerides (ANOVA test: P=0.041 for cholesterol and P=0.032 for triglycerides).

Table III.25: Presentation of cholesterol and triglyceride values related to the grade of vessel blockage

	N	Mean	SD	Standard deviation	95% Cl of the average		Minimum	Maximum
					Lower bond	Upper bond		
Cholesterol Single vessel	226	76.7969	55.89877	3.71833	182.4697	197.1241	80.20	434.70
Double vessel	184	89.9848	190.55558	4.04794	169.2680	224.7015	82.20	2676.20
Triple vessel	214	98.3607	52.77761	3.60780	179.2492	193.4723	80.00	412.00
Total	624	87.7380	112.98397	4.52298	181.8559	199.6201	80.00	2676.20
Triglycerides Single vessel	225	70.4893	228.69948	5.24663	187.4442	247.5345	49.60	2230.50
Double vessel	185	93.8757	102.89508	7.56500	171.9504	201.8010	22.90	686.00
Triple vessel	214	207.4673	111.79019	7.64182	175.4040	205.5306	28.60	894.40
Total	624	88.1460	162.47289	6.50412	186.3733	211.9187	22.90	2230.50

3.5 Relation between arterial hypertension with the vessel blockage in CAD patients

There is no relation between arterial hypertension and vessel blockage in CAD patients (**Fisher's exact test: P=0.385**).

This finding is reflected in the below mentioned table:

Table III.26: Relation between AHT and vessel blockage in CAD patients

Vessel blockage	AHT		Total
	No	Yes	
Single vessel	56	170	226
	38.40%	35.40%	36.10%
Double vessel	47	139	186
	32.20%	29.00%	29.70%
Triple vessel	43	171	214
	29.50%	35.60%	34.20%
Total	146	480	626
	100.00%	100.00%	100.00%

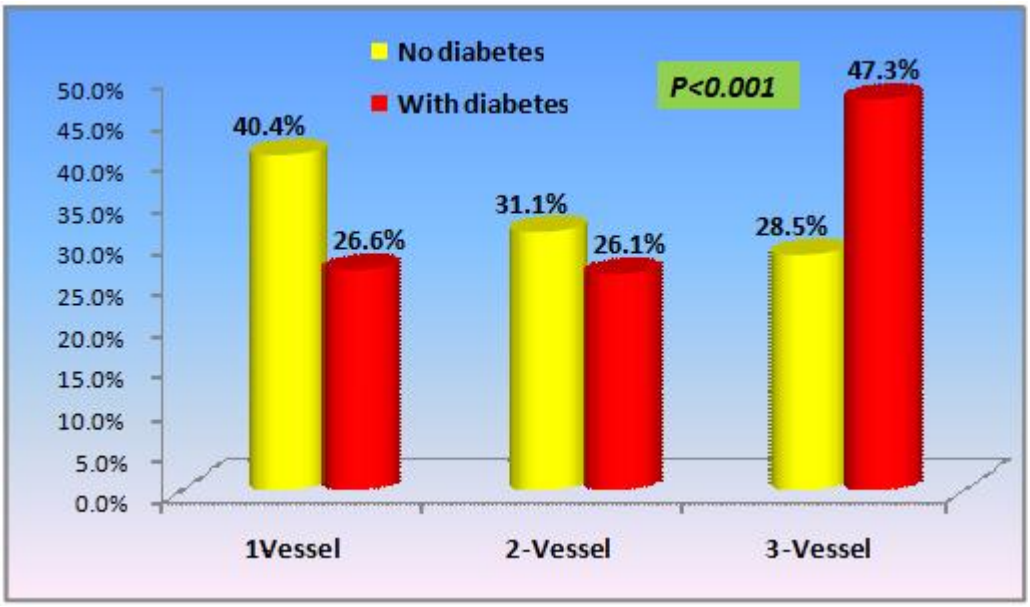
3.6 Relation between diabetes with vessel blockage in CAD patients

On the other hand, there is a significant relation between diabetes and vessel blockage in CAD patients: diabetes prevalence is sensitively increases with the increase of vessel blockage **(Fisher's exact test: P<0.001).**

This finding is reflected in the below mentioned table:

Table III.27: Relation between diabetes and vessel blockage in CAD patients

Vessel blockage	Diabetes		Total
	No	Yes	
Single vessel	177	50	227
	40.40%	26.60%	36.30%
Double vessel	136	49	185
	31.10%	26.10%	29.60%
Triple vessel	125	89	214
	28.50%	47.30%	34.20%
Total	438	188	626
	100.00%	100.00%	100.00%



Graph III.33: Graphical presentation of relation between diabetes and vessel blockage in CAD patients

3.7 Relation of IHD family health history with vessel blockage in CAD patients

On the other hand, there is no significant relation between Ischemic Heart Disease (IHD) family health history and vessel blockage in CAD patients: (**Fisher's exact test: P=0.653**). This finding is reflected in the below mentioned table:

Table III.28: Presentation of IHD family health history and relationship with vessel blockage in CAD patients

Vessel blockage	IHD Family Health History		Total
	No	Yes	
Single vessel	173	54	227
	35.70%	38.60%	36.30%
Double vessel	143	43	186
	29.50%	30.70%	29.80%
Triple vessel	169	43	212
	34.80%	30.70%	33.90%
Total	485	140	625
	100.00%	100.00%	100.00%

4. Discussion

4.1.1 hs-CRP and TNF-alpha role assessment in CAD patients.

The cases examined in this paper, for the assessment component of the risk factor in developing cardiopathy, consisted in a contingent of cardiopathy patients.

There has been carried out an analysis of the risk factors considered as risky ones for CAD in patients having unstable angina and that underwent to the Cathlab examination.

Hence, it turned out by statistical analysis (ANOVA test), that hs-CRP is an independent risk factor in CAD patients and its values are related in linearity with the vessel blockage (p=0.008).

It is considered that inflammation plays a major role in CAD physiopathology.

A large number of papers have shown that the systemic inflammation, assessed through measurement of the C-reactive protein level with high sensitivity, correlates with atherosclerotic diseases prognosis. 3 In more than 25 studies carried out (of the retrospective type), it is clearly reported and showed a very significant and independent relation between CRP high levels in serum and future cardiovascular events. A meta-analysis merging the outcomes of the 14 prospective studies with a total number of 2557 cases and with a follow-up average period of time of 8 years, showed that individuals with CRP values in the third superior level of measurements, have a relative CAD risk in a value of 1.9 compared to those where the CRP level was in the lower level.4

Our outcomes are similar to those of other clinical, laboratory and epidemiological studies whose outcomes suggest that atherosclerosis is a chronically inflammatory status which is developed as a result of the combination of biochemical, physical and eventually infective processes. Obviously, the lab data in these papers (like in ours) as far as it concerns the proteins in the acute phase, serve to discover and evaluate the systemic inflammatory process. In this framework also our outcomes support the idea that the inflammatory process in the vessel walls takes part in the atherosclerotic process. hs-CRP levels correlate with the CAD and coronary events clinical worsening, both in acute and sub acute phases of the myocardial ischemia.5 In a recent study carried out by Zairis et al. it is reported that hs-CRP concentrations correlate with the stenosis complexity scale in ACS patients. In ACS patients, the increment of the CRP levels is associated with the presence of the complex angiographic lesions and the need for revascularization.6

Many epidemiologic data, obtained both in Europe and U.S have sustained the CRP role as a vascular risk biomarker, by indicating that the increased CRP levels among apparently healthy individuals are an important predictor of the future cardiovascular events. By many prospective studies carried out in the world, CRP turns out to be a measurable marker of a hidden systemic inflammation and it is a very powerful predictor of a future heart attack or sudden deaths.

While the CRP levels could increase more than 1000 times as a response to a major infection or traumas, they are stable for a long period of time when measured in asymptomatic adults, whose CRP in levels above the normal one has turned out to be a strong and independent warning of the future vascular events.[7] In addition hs-CRP is being studied even in 302 autopsy cases in males and females where the only inflammatory status was atherosclerosis. The lowest serum level of hs-CRP was found in individuals passed away by non cardiac causes.[8] The contrary is seen as far as it concerns the TNF-alpha serum level and the relation of this one with the scale of the vessel blockage.

Hence in our study it turned out a statistically non-significant relation between TNF-alpha and vessel blockage in CAD patients (ANOVA test: p= 0.156). But it has been noticed an inconsistent relation of the last one with the vessel blockage scale. TNF-alpha mean values turned out to be very high in triple vessel blockage, but its mean values were lower in double vessel blockage compared to TNF-alpha mean values in single vessel blockage.

TNF-alpha is a cytokine with a large scale proinflammatory activity. TNF-alpha is initially produced by monocytes, macrophages while an interesting quantity is secreted by other cell types. Disorders in TNF-alpha metabolism are related to metabolic disorders like obesity and insulin resistance. High plasmatic levels are found in patients with premature CAD.

In a study carried out in a Asiatic population, it has been demonstrated that TNF-alpha high levels in serum were associated with a high risk for ischemic strokes. The opposite turned out to be in a prospective study in UK where TNF-alpha levels did not correlate with the ischemic stroke risk, a fact that is similar even in our study where the degree of the vessel blockage does not consistently correlate with TNF-alpha values.

Polymorphism itself that characterizes TNF-alpha genetic variants as well as the interaction between the environmental and genetic are presumed to define the TNF-alpha serum levels.[9,10]

Studies have shown that certain statine types like for instance: atorvastatin, simvastatin and ACEI(angiotensin-converting enzyme inhibitor) quinapril, lower the circulating TNF-alpha levels and do improve the endothelial function in patients with diabetes type 2, heart congestive diseases, RA

or hyperlipidemy.[11-13] In the CAD patients group take into examination, there could be individual which make even use of statines or ACEI which could have possibly influenced the TNF-alpha as well.

It still remains unclear from the studies whether the high TNF-alpha levels in the serum of the patients suffering from atherosclerosis derive from the atherosclerosis plaques or have non vascular origins.

There are a lot of prospective studies, with respect to the healthy population, showing that the CRP levels are an independent risk factor of the atherosclerotic process and simultaneously a predictor of the future cardiovascular events. 14 These studies have involved both sexes, European and non-European of all ages.[15] Moreover, CRP is assessed also as a predictor of the cerebral strokes and of the peripheral arterial diseases.[16] CRP turns out to be interestingly slightly correlated with the size of the atherosclerotic process like : carotid intima thickness or the extent of the atherosclerotic process. Also there are other studies demonstrating that the CRP level increase goes in parallel with the atherosclerosis size.[17]

hs-CRP dosage is not valid in patients with confirmed inflammatory processes since in many studies almost 2% of the patients contain CRP values over 2 mg/dl, where these values are usually associated with other inflammatory processes. Latest information has clearly revealed that the increase of CRP levels within normal levels is associated with future coronary events in apparently healthy individuals. It is very interesting the theory standing behind this correlation. We could say that CAD, based upon what we described above, is considered today as a demonstration of an inflammatory process. Patients, which are more likely to have acute ischemic events, have unstable atherosclerotic plaques. These patients are subject to a high risk of developing fissures, ruptures as well as thrombogenesis. These occurrences, with time lead to acute thrombotic blockages in the most part of the coronary vessels and in the increase of the inflammatory process. This inflammation does not stay localized only in damaged vessels but appears also systematically by the increase of the inflammation level markers like: cytokines and CRP. Indeed in many high risk patients suffering from ACS (Acute Coronary Syndrome) are being mostly manifested signs of a systemic inflammation rather than localized ones 18.

As a conclusion, the use of an easily measurable systemic inflammatory marker like hs-CRP with a relatively high half life of 19Hrs and independent from the circadian rhythm, could define which patients are in higher atherosclerotic risk and who among CAD patients have the higher risk to develop future cardiovascular events.[19]

References

[1] Ross R, *N Engl J Med*, 1999;340(2):115–26.
[2] Kaperonis EA, Liapis CD, Kakisis JD, et al., *Eur J Vasc Endovasc Surg*, 2006;31(4):386–93.
[3] Ridker PM. High –sensitivity C- reactive protein ;adjunct for global risk assessment in the primary prevention of cardiovascular disease.Circulation.2001;103(13):1813-8.
[4] Danesh J,et al Brit Med J,2000;321:199-204
[5] Zairis M,Papadaki OA,Monousakis S, Thoma MA, Beldekos DJ, Olympios CD, , et al. C-reactive protein and multriple complex coronary artery plaques with unstable angina .Atherosclerosis 2002;164:355-9.
[6] Moukarbel GU, Arnaout MS, Alan SE, .C-Reactive protein is marker for a complex culprit lesion anatomy in unstable angina .Clin cardiol 2001;24:506-10. .
[7] Sakkinen P, Abbot RD, Curb JD, et al .C-reactive protein and myocardial infarction.J Clin Epidemiol.2002;55:445-451.
[8] Burke AP, Tracy RP,Kolodgie F,et al. Elevated C-reactive protein values and atherosclerosis in sudden coronary death:association with different pathologies .Circulation .2002:105:2019-2023.
[9] Polymorphiosm of (TNF-alfa) gene promoter circulating TNF-alfa level , and cardiovascular risk factors for ischemic stroke :Guanlin Cui et al.Journal of Neuroinflammatory 2012,9:235.
[10] Jeffers BJ,Wincup PH, Welsh .P,Wannamethee SG, Rumley A, Lennon LT, Thomson AG, et al.Circulating TNF-alpha levels in older men and women do not show independent prospective relations with MI stroke.Atherosclerosis 2009;205:302-308
[11] Marketou M.E., Zacharis E. A., Nikitovic D., et al .Early effects of simvastatin versus atorvastatin on oxidative stress and proinflammatory cytokines in hyperlipidemic subjects.Angiology.2006;57:211-218.
[12] Koh K .K.,Son J .W.,Ahn J.Y., et al.Vascular effects of diet and statin in hypercholesterolemic patients .Int .J.Cardiol.2004;95:185-191.
[13] Economides P.A., Caselli A., Tiani E., Khaodhiar L., Horton E.S., Veves A. The effects of atorvastatin on endothelial function in diabetic patients and subjects at risk for type 2 diabetes .J. Clin .Endocrinol.Metab.2004;89:740-747.
[14] Peter Libby,Paul M. Ridker,Attilio Maseri. Inflammation and Atherosclerosis American Heart Association Circulation;105:1135-1143;2002.
[15] C-reactive protein and cardiovascular disease: a review of risk prediction and interventions Sarah de Ferranti, Nader Rifai. Clinica Chimica Acta 317;2002.
[16] Köenig W, Sund M, Fröhlich M, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation;99:237-242; 1999.
[17] Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med;347:1557-1565; 2002.
[18] Graham IM, Daly Le Refsum HM et al. Plasma homocysteine as risk factor for vascular disease. the Europian Concerted Action Project. JAMA 277: 1775 - 81 ;1997.
[19] Naldi L.Epidemiology of Psoriasis.Curr Drug Targets Inflamm.Allergy 2004;3(2):121-8