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Serum CXCL10 and CXCL12 chemokine levels are associated with the severity of coronary artery disease and coronary artery occlusion

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ABSTRACT

Background: Cardiovascular disease constitutes a major cause of death worldwide. Inflammation plays an important role in atherosclerosis formation, coronary artery disease progression, acute coronary thrombosis and occlusion. Chemokines are inflammatory mediators disposing several bio-functions, as leukocyte migration towards inflammatory signals and vascular injuries. The present study was designed to evaluate the potential correlation between serum levels of chemokines CXCL-10 and CXCL-12 and the degree of coronary artery occlusion.
Methods: Eighty eight patient candidates for coronary angiography with coronary artery disease symptoms and potentially high risk of coronary artery occlusion were recruited. Chemokine serum levels were measured with the ELISA method and patients underwent coronary angiography. All patients with coronary artery disease (CAD) were divided into four groups according to the Gensini score. Data were presented as mean ± SD. All P values <0.05 were considered significant.
Results: Our demographic data showed that of the 88 patients, 46 were male and 42 female. The mean age of patients was 57.95 ± 11.13. Following increased coronary artery occlusion the serum levels of chemokines were significantly increased (CXCL-10 and CXCL-12; $P \leq 0.0001$ and $P < 0.0001$, respectively).
Conclusion: In this novel study, a significant correlation between the serum levels of CXCL-10 and CXCL-12 and the severity of coronary artery occlusion was found. This could be attributed to the role of these chemokines in the processes of angiogenesis and angiostasis, a biological phenomenon that can play key role in the development of collateral circulation.

1. Introduction

Cardiovascular diseases are major causes of death in most countries across the world [1,2] Coronary artery disease (CAD) constitutes the most frequent cause of death in the USA [3]. Death due to cardiovascular disease occurs every 36 s [4]. According to the latest reports from the ministry of health of Iran, CAD is associated with a high mortality rate in patients aged over 35 years [5]. However, during the last decades the coronary artery disease mortality rate has significantly decreased in developed countries, fact that could be attributed to both primary and secondary care and prevention programs [6]. Several risk factors, such as family history, increased lipid levels, hypertension, smoking, diabetes mellitus, and obesity, are involved in CAD. Additional parameters, including fibrinogen levels, status of inflammation biomarkers, C-Reactive Protein (CRP), IL-1B and a variety of infectious bacteria such as chlamydia and helicobacter pylori have been also incriminated, as playing a role in cardiovascular disorders [7]. Furthermore, inflammation plays a crucial role in both atherosclerosis and acute coronary

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syndromes. Atherosclerosis is a progressive disease with inflammatory background, as white blood cells (WBC) contribute to the initiation, continuation, and exacerbation of the disease [8–10]. Chemokines belong to a diverse subcategory of the larger family of cytokines that display a wide spectrum of bio-functions. Notably, chemokines constitute the main immune cells that trans-migrate towards infection, inflammation, and tissue traumatic injury locations [11,12]. In addition to their roles in the inflammation processes and mobilization of immune cells, chemokines participate in other significant functions, as either the initiation new blood vessel formation, namely angiogenesis or the inhibition of new blood vessel formation, namely angiostasis [13]. More than 50 chemokines and at least 20 chemokine receptors have been identified [14]. Chemokines, due to similarities in their amino acid sequences (patterns of paired cysteine (C) repeats and internal disulphide bridges) have been categorized on a structural basis into four major classes, as C, CC, CX3C and finally CXC subclasses [15,16]. Chemokine CXC classes such as CXCL-10 and CXCL-12 display vital importance in the process of angiogenesis and angiostasis [14,17]. According to the presence or absence of an ELR (glutamine-leucine-arginine) motif immediately adjacent to CXC, the CXC chemokines are further divided in two subgroups, ELR^+ and ELR^-. ELR^+ such as CXCL1, CXCL2 and CXCL3 are all chemoattractant for neutrophils. The ELR^- subgroup of CXC chemokines such as CXCL10, and CXCL12 are chemoattractant for lymphocytes, monocytes and NK cells [18,19].

While several chemokine CXC classes have been proven to be associated with the severity of various inflammatory conditions, including atopic dermatitis, alopecia areata [20], Behcet's disease, diabetes [17,18,21], infections [22], leukemias [23], prostate cancer, sickle cell disease [24], systemic lupus erythematosus and tick-borne encephalitis, their relationship with atherosclerotic coronary artery disease has not been elucidated and remains unclear. Whether the serum levels of chemokine CXC classes are associated with the severity and prognosis of CAD was the aim of this study. Especially, we measured the levels of angiostatic (anti-angiogenic) CXCL-10 and the angiogenic CXCL-12 and their balance in order to clarify their role in CAD patients who underwent angiography.

2. Material and methods

2.1. Patients

This cross-sectional study was performed on 88 patients and who candidates were of underwent angiography and presented coronary artery disease signs or potentially high risk of coronary artery occlusion. Although, we enrolled 100 patients, six of them were withdrawn from the study due to myocarditis, two due to liver diseases, and four patients due to use lipid-lowering drugs. The relationship between chemokines CXCL-10 and CXCL-12 and the degree of coronary artery occlusion was evaluated in patients regarding age, gender, hyperlipidemia, diabetes, weight, body mass index (BMI), smoking, hypertension and Gensini score. The Gensini score was defined as narrowing of the lumen

of coronary arteries according to the previous description [25]. The hypertension was defined as having a blood pressure higher than 140 mm Hg over 90 mm Hg or taking antihypertensive therapy. Hyperlipidemia is characterized as showing total cholesterol ≥200 mg/dL or triglycerides ≥150 mg/dL or LDL ≥130 mg/dL or receiving treatment. The diabetes mellitus was diagnosed in patients who had blood glucose level of 200 mg/dL or more, HbA1c in excess of 6.5%, or those receiving antidiabetic drugs as confirmed by medical history taking, according to the guidelines of the American Diabetes Association [26]. The inclusion criteria for the study were signs and symptoms of ischemic heart disease and CAD in coronary angiography. The exclusion criteria included previous history of myocardial infarction, valvular heart disease, myocarditis, liver disease, administration of lipid-lowering drugs, and a history of acute infection during the previous two weeks.

Upon entering the study, the gender, blood pressure, height, and weight of all the patients who met the inclusion criteria were recorded. Patients underwent coronary angiography using the Seldinger's method. Films were evaluated by expert cardiologists and the coronary score (Gensini score) was determined, according to the location and severity of stenosis, as previously described by Gensini [25]. The invasive coronary angiography (ICA) was undertaken according to the standard methods. Angiograms were determined by expert cardiology specialists and all of the available coronary segments were defined in accordance with the American Heart Association guidelines [27]. The same segmental model using identical description was applied for ICA. Consequently, all of segments were visually divided as normal (no atherosclerosis or minor wall irregularities with <20% luminal narrowing) or abnormal (presence of stenosis >20% luminal narrowing). All segments were visually scored as abnormal and quantified employing a validated quantitative coronary angiography (QCA) software package (QAngioXA 6.0, CA-CMS, Medis Medical Imaging Systems, Leiden, The Netherlands). Each separate segment was then evaluated for the presence of significant stenosis by determining the presence of >50 and 70% luminal diameter reduction in the angiographic view with most severe luminal narrowing. Obstructive CAD was defined as luminal narrowing of >50% on QCA analysis.

After determination of coronary artery occlusion (0, 25, 50, 75, 90, 99, 100), its equivalent was respectively (0, 1, 2, 4, 8, 16, 32) according to the Gensini system. In respect to the location of the stenosis and the vessel involvement, a coefficient was considered. After multiplying the Gensini score by the related coefficient, the sum of obtained values, represented the coronary artery occlusion index (the Gensini score). Finally, patients were divided into four groups, according to the obtained Gensini score as follows: the first group had a score of 0, the second group showed scores of 1–25, the third group exhibited scores of 26–61, and, finally, the fourth group displayed a score of 62 and higher [25].

2.2. Chemokine assay

Following blood collection, the separated serum specimens were immediately frozen and stored at −80 °C until the time of the assay. The CXCL10 (catalog number DIP100) and CXCL12 (catalog number DSA00) serum levels were measured by ELISA (R&D system, Minneapolis, USA). All of assays were conducted according to manufacturer's guidelines. The sensitivity of the kits was 4.46 pg/mL and 47 pg/mL, respectively. Inter- and intra-assay assessments of reliability of the kits were conducted (CV < 15% and CV < 0.05%, respectively).

2.3. Ethics Committee approval and patient consent

Only patients willing to participate in the study and who signed a declaration of consent were included in this study. The approval of the Ethical Committee was obtained with a number of IR.RUMS.REC.1395.56 and all names have been changed to numbers.

2.4. Statistical analysis

Data were analyzed using SPSS software (version 18, SPSS Inc., Chicago, IL, USA). Quantitative data were presented as Mean ± SD. For comparison of the underlying factors, ANOVA, *t*-test, and chi-square test were used. The correlation between serum levels of chemokines and the degree of coronary stenosis and also lipid profile (triglyceride, cholesterol, HDL, LDL) was determined using scatter plot and Pearson correlation coefficient. All $P < 0.05$ were considered significant.

3. Results

We examined 88 CAD patients with an average age of 57.95 ± 11.13 years. Forty six patients (52.27%) were male and 42 (47.73%) were female. Thirty nine (44.31%) were hypertensive and 49 (55.69%) were not hypertensive. Hyperlipidemia, diabetes and heavy cigarette smoking were present in 36 (40.90%), 23 (26.13%) and 17 (19.31%) patients respectively, as shown in Table 1. As analyzed, our findings indicated that the serum level of triglycerides was 178.98 ± 98.41, total cholesterol was 191.4 ± 51.91, HDL (high density lipid) was 37.8 ± 11.11 and LDL (low density lipid) was 119.3 ± 44.81. Interestingly, in males, the angiogenic CXCL-12 levels were significantly higher than in females (282.57 ± 172.64 pg/mL) versus (206.51 ± 144.42 pg/mL), respectively; $P < 0.025$, $df = 90$, $t = 2.27$.

In diabetics, the angiostatic CXCL-10 levels demonstrated a statistically significant increase compared to non-diabetic patients (442.84 ± 263.57 pg/mL) versus (310.54 ± 198.5 pg/mL); $P < 0.012$, $df = 90$, $t = 2.56$.

In parallel with the weight increments, CXCL-10 and CXCL-12 levels were significantly increased ($P = 0.007$ and $P < 0.011$, respectively, Table 1).

In accordance with BMI increase, CXCL-10 and CXCL-12 chemokines demonstrated a statistically significant elevation ($P < 0.005$ and $P < 0.021$) as presented in Table 1.

In the studied patients, there were no significant correlation between both CXCL-10 and CXCL-12 and lipid profile as presented in Table 2.

As clearly shown in Fig. 1a, correlation was observed between CXCL10 and CXCL12 with Gensini score (Fig. 1a). There was also a correlation between the CXCL10 and CXCL12 with BMI (Fig. 1b). We have found a correlation between the weight of patients and the studied CXC chemokines, CXCL10 and CXCL12 (Fig. 1c). It appears that the correlation between CXCL10 and Gensini score is more significant than the

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Table 1
Demonstrates the demographics and some clinical characteristics of patients.

Demographics	Number (percentage) Gensini score				Total
Age of participants	G1 (0)	G2 (1–25)	G3(26–61)	G4 (>61)	
Mean (rang)	55.62 (42–70)	56.63 (32–79)	63.95 (43–83)	60.12 (42–71)	57.95 (14–83)
BMI	G1 (0)	G2 (1–25)	G3(26–61)	G4 (>61)	24.84 (13.84–60.23)
Mean (rang)	23.28 (13.84–30.08)	24.84 (19.03–32.76)	24.28 (20.20–31.64)	29.79 (18.52–60.23)	
Gender of participants	G1 (0)	G2 (1–25)	G3(26–61)	G4 (>61)	
Male	6 (13%)	21 (45.7%)	14 (10.5%)	5 (10.9%)	46 (100%)
Female	10 (23.8%)	23 (54.8%)	6 (14.3%)	3 (7.1%)	42 (100%)
Hypertension history	G1 (0)	G2 (1–25)	G3(26–61)	G4 (>61)	
Hypertensive	6 (15.4%)	18 (46.2%)	10 (25.6%)	5 (12.8%)	39 (100%)
Non-hypertensive	10 (20.4%)	26 (53.1%)	10 (20.4%)	3 (6.1%)	49 (100%)
Hyperlipidemia history	G1 (0)	G2 (1–25)	G3(26–61)	G4 (>61)	
Hyperlipidemia	5 (13.9%)	19 (52.8%)	7 (19.4%)	5 (13.9%)	36 (100%)
Non-hyperlipidemia	11 (21.2%)	25 (48.1%)	13 (25%)	3 (5.8%)	52 (100%)
Diabetes history	G1 (0)	G2 (1–25)	G3(26–61)	G4 (>61)	
Diabetic	4 (17.4%)	7 (30.4%)	8 (34.8%)	4 (17.4%)	23 (100%)
Non-diabetic	12 (18.5%)	37 (56.9%)	12 (18.5%)	4 (6.2%)	65 (100%)
Smoking history	G1 (0)	G2 (1–25)	G3(26–61)	G4 (>61)	
Smoker	1 (5.9%)	11 (64.7%)	3 (17.6%)	2 (11.8%)	17 (100%)
Non-smoker	15 (21.1%)	33 (46.5%)	17 (23.9%)	6 (8.5%)	71 (100%)
Total	16 (18.2%)	44 (50%)	20 (22.7%)	8 (9.1%)	88 (100%)

CXCL12 and overall CXC10 is more associated with other parameters like weight and BMI. Therefore, the severity of the stenosis could be predictable, based on these chemokines serum level in the presented model. Notably, both CXCL-10 and CXCL-12 levels ($P \leq 0.0001$ and $P < 0.0001$, respectively) were significantly elevated in higher Gensini scores, depicting a strong correlation between these inflammatory mediators and coronary artery disease severity. The CXCL10 level in patients with the Gensini score of 1 was 142.675 ± 15.00256 μg/mL, in Gensini score 2 was 256.025 ± 55.54539 μg/mL, in Gensini score 3 was 521.16 ± 79.95616 pg/mL and patients with Gensini score of 4 had 901.5875 ± 54.91121 pg/mL (Fig. 2). We observed that the CXCL12 serum level in patients with the Gensini score of 1 was 108.75 ± 22.0106 μg/mL, in Gensini score 2 was 174.4091 ± 66.78265 μg/mL, in Gensini score 3 was 444.7 ± 69.01266 pg/mL and Gensini score of 4 had 502 ± 177.0585 pg/mL (Fig. 3).

4. Discussion

In the present study, both CXCL-10 and CXCL-12 chemokines were significantly elevated in men depicting the perpetual interplay between angiogenesis balance, inflammation and atherosclerosis. It has been found that testosterone hormones and sex hormone-binding globulin, through their impact on angiogenic CXCL-12 affect the pathogenesis of CAD inducing effectively CXCL-12 chemokine expression and production [28]. Previous studies have demonstrated that the increased levels of angiostatic CXCL-10 facilitate the risk of a chronic heart disease [29] contributing to the induction of vascular calcification [30]. It is evident that the risk of arterial calcification and stiffness development progresses with age. Other studies have shown that, the blood pressure reduction is associated with further depletion of CXCL-10 serum levels displaying a beneficial effect on inflammatory mediators [31]. A pivotal role of CXCL-10 in the formation and rupture of plaques has already been established [32]. It has also been shown that several metabolic disturbances, causing diabetes, endothelial cell dysfunction and acute vascular inflammation, contribute ultimately to the development of atherosclerotic coronary arteries and chemokines facilitate these activities through their anti-sclerotic functions [33].

In our study, non-smokers exhibited higher chemokine serum levels than smokers; however, the difference was not significant. Non-smokers, compared to smokers, had relatively higher levels of angiogenic chemokines. There was not any difference in chemokine levels between hypertensive and non-hypertensive patients and between hyperlipidemic and non-hyperlipidemic patients. Angiogenic chemokines, particularly CXCL-12, are involved in several biofunctions such as angiogenesis [34,35] survival of myogenic cells [36], prevention of apoptosis [37], increased survival of myocardial cells during ischemia [38] and recovery from a heart attack [39]. One of the beneficial effects of quitting smoking is the enhancement of angiogenic chemokines serum levels. This phenomenon plays important role in parallel with other issues such as oxidative stress reduction [40,41]. As far as we know, there is no evidence of the cigarette and nicotine effect on chemokine production in the literature, fact that renders our findings novel.

It appears that with BMI elevation, serum levels of chemokines in both categories were increased. This effect was more evident in angiostatic CXCL-1compared to the angiogenic chemokine CXCL-12. Therefore, the negative effect of weight gain, correlated with hyperlipidemia, decreased physical activity, and increased oxidative stress can be translated into coronary atherosclerosis progression. However, this difference was significant in both chemokines highlighting the strong correlation between angiogenesis/angiostasis imbalance and atherosclerosis evolution.

To the best of our knowledge, this is the first study that addresses a link between the angiogenesis related chemokines and CAD, in particular the levels of coronary artery occlusion based on the Gensini score. The main novel point was the correlation between the concentrations of CXCL10 and CXCL12 chemokines and coronary artery occlusion. The serum levels of both types of chemokines were increased in accordance

Table 2
Shows correlation between triglyceride, cholesterol, HDL, LDL and serum levels of chemokines.

Chemokine	Triglyceride	Cholesterol	HDL	LDL
CXCL-10	Pearson correlation 0.346 P = 0.327	Pearson correlation: −0.028 P = 0.938	Pearson correlation: 0.333 P = 0.347	Pearson correlation: −0.730 P = 841
CXCL-12	Pearson correlation: −0.920 P = 0.801	Pearson correlation: 0.363 P = 0.303	Pearson correlation: 0.389 P = 267	Pearson correlation: 0.357 P = 0.311

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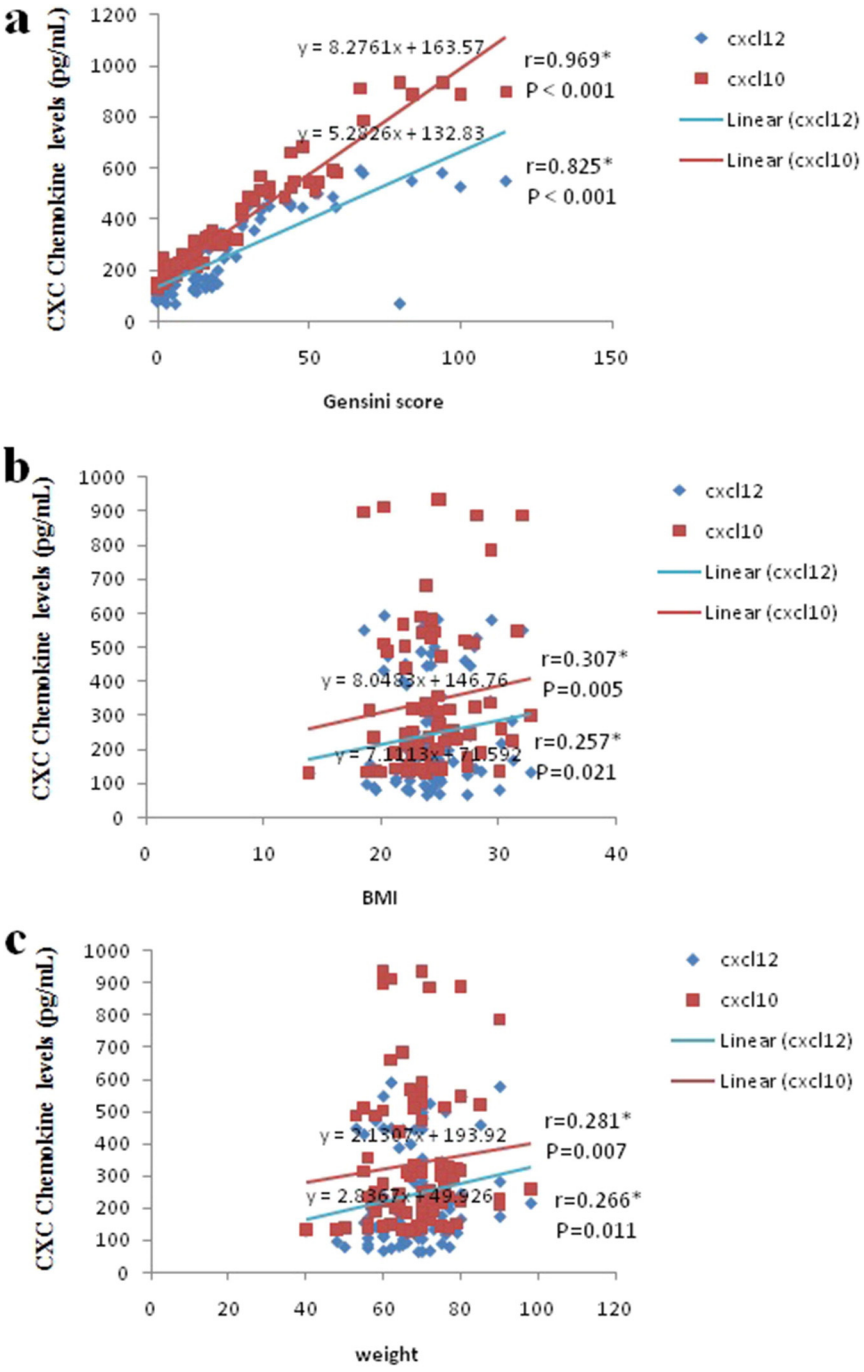

Fig. 1. Demonstrates correlation between the CXC chemokines (CXCL10 and CXCL12) with Gensini score, BMI and weight. a) Scatter plot of CXCL10, CXCL12 against Gensini score. b) Scatter plot of CXCL10, CXCL12 against BMI. c) Scatter plot of CXCL10, CXCL12 against weight. r = Pearson correlation coefficient and $P < 0.05$ considered significant. Data are for 88 unrelated CAD patients.

with the severity of coronary artery stenosis and occlusion. It appears that there is an intensive competition between these two chemokines and each chemokine is increased in an attempt to influence angiogenesis/angiostasis balance. This can define the degree of coronary atherogenesis, neointimal hyperplasia, atherosclerotic plaque formation and finally coronary artery occlusion rate. In the groups of CAD patients presenting with various degrees of occlusion, there was a significant difference between groups with different Genisini score. The only exception was regarding CXCL-12, in which no significant difference was observed between groups 3 and 4 in terms of coronary artery disease. Interestingly, beyond a certain degree of occlusion, these chemokines were not increased as intensely as before. Given the important and influential effects of CXCL12 on vascularization [42], on increased myocardial cell survival in ischemic conditions [43,44], on stem cells in the affected area [36], on apoptosis prevention [39] and on improvement of left ventricular ejection fraction in patients with myocardial infarction [44], angiogenesis as well as vascular stabilization and reconstruction, could be achieved if the CXCL12 activation rate is equivalent to that as in a severe occlusion. Previous studies have also shown that in addition to CXCL-16 as a CXC chemokine which was strongly linked with CAD [45], the CCL2 level as the member of the CC chemokines group was also higher in patients with CAD than in normal individuals [46]. It should be noted that several studies have shown the role of cytokines such as TNF-α, IL-27, CXCL-8, and CRP in the degree of coronary artery occlusion [47,48].

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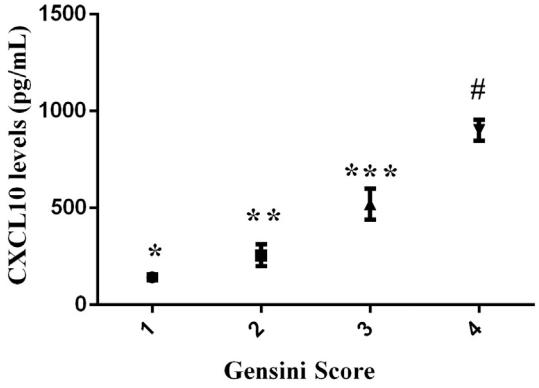

Fig. 2. Demonstrates the CXCL10 level according to the Gensini score. Patients underwent angiography and related Gensini scores were calculated. Serum samples were isolated and subjected to ELISA for determining CXCL10. Results are expressed as mean ± SD for 88 unrelated patients. * = Significant difference with Gennesi groups 2, 3, 4. ** = Significant difference with Gennesi groups 3, 4. *** = Significant difference with Gennesi groups 4.

Since chemokines are a group of cytokines, they can also have a key role in coronary artery occlusion.

Our study was limited to the ethical issue for obtaining clinical tissue samples from the patient vessels for examination of either chemokines or their receptors at mRNA and protein level in injured areas. We must emphasized that, despite great promises in the treatment of arterial diseases with stem cell therapy based on molecular cell interventions, the long-term effects of cell types are still unknown [49].

5. Conclusion

Nevertheless, if the balance between the two measured chemokines could be adjusted so that the influence of angiogenic chemokine would be greater than angiostatic chemokine, then enhancement of collateral vessel creation, reconstruction of coronary arterial tree and further improvement and increase of the efficiency of these vessels could become reality in the near future.

Declaration and verifications

All the authors imply that the work described has not been published previously and they also, imply that if it accepted, it will not be published elsewhere in the same form, in English or in any other language.

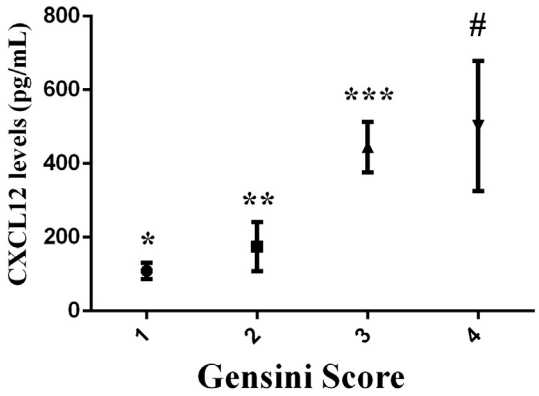

Fig. 3. Demonstrates the CXCL12 level according to the Gensini score. Patients underwent angiography and related Gensini scores were calculated. Serum samples were isolated and subjected to ELISA for determining CXCL12. Results are expressed as mean ± SD for 88 unrelated patients. * = Significant difference with Gennesi groups 2, 3, 4. ** = Significant difference with Gennesi groups 3, 4. *** = Significant difference with Gennesi groups 4.

Conflict of interest

All authors have reported that they have no industry relationships or other conflicts of interest relevant to the contents of this paper to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.02.011.

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