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Expansion of CD4⁺CD28^{null} T Lymphocytes Contributes to Coronary Artery Diseases in Rheumatoid Arthritis Patients

M. E. Ansary¹, E. A. Ghaffer², N. M. Gendy¹, N. S. Hasan², M. M. Sedkey³

Background: The expanded CD4⁺ clonotype T cell subset lacking surface CD28 has been suggested to predispose rheumatoid arthritis (RA) patients to develop more aggressive disease including extra-articular manifestations and CAD. **Patients and Methods:** The number of circulating CD4⁺CD28^{null} T cells was evaluated in 42 RA and 10 control subjects by 2-color FACSort flow cytometer, patients underwent evaluation of joint involvement, extra-articular manifestations, and CAD association. **Results:** The frequency of CD4⁺CD28^{null} cells was significantly higher in patients than in control subjects. RA patients with persistent expansion of circulating CD4⁺CD28^{null} cells had more marked increase of extra-articular manifestation ($P = 0.000$) and CAD ($P = 0.000$). Expansion of circulating CD4⁺CD28^{null} T cells correlated significantly with elevated ESR, triglycerides, and seronegative RF. **Conclusion:** Circulating CD4⁺CD28^{null} T lymphocytes are increased in RA. Patients with persistent CD4⁺CD28^{null} T cell expansion show more extra-articular manifestation and CAD. These findings suggest that increased CD4⁺CD28^{null} T cell expansion, ESR, and triglyceride levels together with seronegative RF can serve as markers to help identify patients with rheumatoid arthritis who are at risk of developing CAD. Moreover, the correlation between CD4⁺CD28^{null} T cell expansion, ESR, and triglyceride levels together with seronegative RF may be of interest for possible innovative predictive and diagnostic strategies in cardiovascular diseases. *J Clin Basic Cardiol 2012; 15 (online): 2–6.*

Key words: CD4⁺, CD28^{null}, RA, extra-articular manifestations, CAD

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by uncontrolled proliferation of synovial tissue and a wide array of multi-system affection [1].

Rheumatoid arthritis is one of the best characterized autoimmune diseases associated with increased frequencies of CD4⁺CD28^{null} T cells [2–4]. Studies in patients with RA showed CD4⁺CD28^{null} T cells to be increased in > 1/3 of patients [2, 5]. Furthermore, expansion of the CD4⁺CD28^{null} T cell subset correlated directly with an increased frequency of extra-articular involvement like rheumatoid vasculitis and the clinical severity of the disease [3, 4]. These results suggest that the expansion of CD4⁺CD28^{null} T cells does not represent just an epiphenomenon but could play a critical role in the pathogenesis of the disease. Interestingly, in contrast to classical CD4⁺CD28⁺ T lymphocytes, CD4⁺CD28^{null} T cells express CX3CR1 which provides signals that support the activation of these cells in vitro [6]. Compared to CD28 T lymphocytes, CD4⁺CD28^{null} T cells isolated from patients with RA induced a significantly higher proliferation of synovioyte lines established from rheumatoid synovium [7]. This effect was mediated through CX3CR1 and amplified by the production of TNF- α from CD4⁺CD28^{null} T cells. Excessive proliferation of synovial fibroblasts causes bone and cartilage destruction in RA. Therefore, these in vitro studies suggest that CD28^{null} T cells promote bone and cartilage destruction in RA.

Recent discoveries highlighting the role of inflammation and immune responses in atherosclerosis have led to a better understanding of the mechanisms underlying CAD development and novel clinical approaches to this disease [8–10].

T lymphocytes, the main “soldiers” of the adaptive immune system, are consistently found in atherosclerotic lesions and contribute to their growth and activity [11]. At the early stages of atherosclerosis, T cells are involved in the initiation and progression of the disease, while at more advanced stages they contribute to the destabilization of atherosclerotic lesions [12, 13].

Most of the T cells present in atherosclerotic plaques are CD4 helper T lymphocytes [14]. Detailed analysis of CD4 T cells in CAD revealed the expansion of an unusual subset of

lymphocytes, characterized by the lack of the CD28 co-stimulatory receptor and therefore named CD4⁺CD28^{null} T cells [15]. Recent studies suggested that CD4⁺CD28^{null} T cells mediate plaque instability and recurrence of acute coronary events [16].

Complications of rheumatoid arthritis may begin to develop within months of presentation; therefore, early referral to or consultation with a rheumatologist for initiation of treatment with disease-modifying anti-rheumatic drugs is recommended, including tumor necrosis factor inhibitors, non-steroidal anti-inflammatory drugs, and corticosteroids, non-pharmacologic modalities are useful as well. Patients who do not respond well to a single disease-modifying drug may be candidates for combination therapy [17]. Moreover, advances in clinical research suggest that the inflammatory and cytotoxic function of CD4⁺CD28^{null} T cells can be inhibited by blocking OX40 and 4 to 1BB co-stimulatory receptors. Modulation of co-stimulatory receptors may allow specific targeting of this cell subset and may improve survival of ACS patients [18].

Patients and Methods

Study Population

42 patients (35 women, 7 men, aged 25–55 years, mean 41 \pm 10 years) with rheumatoid arthritis diagnosed according to the criteria of the American College of Rheumatology were included in the study. Disease duration was 2–13 years (mean 6 \pm 2.5 years). Patients were recruited from the outpatient clinic of the Department of Rheumatology and Physical Medicine, Kasr El Aini University Hospital, Cairo, Egypt.

The control group consisted of 10 healthy subjects (8 women and 2 men, aged 29–65 years, mean age 51 years).

Patient consent was obtained using the form approved by the Ethics Committee of the National Research Center.

Laboratory and Clinical Examination

Subjects underwent routine Hb, ESR, CRP, and lipid profile blood analysis in addition to antinuclear antibodies. In all patients, X-rays were made of the chest, hands, feet, and, when

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Table 1. Clinical characteristics of patients with RA subdivided into groups.

	Group 1	Group 2	Group 3	p
n	10	12	20	–
Age of onset (years)	39.6 ± 11.4	43 ± 8.2	40.8 ± 10.8	0.727
HB (g/dl)	12.7 ± 0.7	12.6 ± 0.5	11.8 ± 1.2	0.023*
Total cholesterol (mg/dl)	204.8 ± 41	204 ± 39.3	194.4 ± 35.4	0.699
HDL (mg/dl)	39.7 ± 1.1	38.9 ± 2.1	38.3 ± 3.2	0.389
LDL (mg/dl)	128.1 ± 39	134.3 ± 37.7	116.6 ± 35.2	0.404
TG (mg/dl)	167.5 ± 54.1	156.2 ± 35.3	194.8 ± 35.1	0.031*
ESR (1 st hour)	23.3 ± 11	24.4 ± 7.3	40.8 ± 24.6	0.019*
Disease duration (years)	5.6 ± 2.1	6.1 ± 1.5	6.3 ± 3.2	0.759
CD4 ⁺ CD28 ⁻ < 15 %	11.7 ± 2	11.3 ± 2	10.1 ± 3.2	0.000*
CD4 ⁺ CD28 ⁻ ≥ 15 %	21.8 ± 3	29.6 ± 5.4	44.5 ± 9.8	0.000*

Data are expressed as mean ± standard deviation.

* p < 0.05 means significant result.

Table 2. Comparison of the expansion of CD4⁺CD28⁺ and CD4⁺CD28^{null} T lymphocytes between RA patient groups and healthy controls

	Group 1	Group 2	Group 3	Controls	p
n	10	12	20	10	–
CD4 ⁺ CD28 ⁻ < 15 %	11.7 ± 2	11.3 ± 2	10.1 ± 3.2	10.5 ± 2.9	0.903
CD4 ⁺ CD28 ⁻ ≥ 15 %	21.8 ± 3	29.6 ± 5.4	44.5 ± 9.8	15.6 ± 0.56	0.000*

Data are expressed as mean ± standard deviation.

* p < 0.05 means significant result.

required, other joints. Evaluation included physical examinations with attention to patterns of joint involvement, presence of nodules, and other extra-articular features such as anemia, secondary Sjogren's, pulmonary affection, dryness of eyes, coronary artery disease, and laboratory features such as erythrocyte sedimentation rate and rheumatoid factor. To examine whether the presence of large numbers of CD4⁺CD28^{null} T cells in patients with RA is predictive of disease manifestation, the patients were allocated according to their disease pattern as follows:

- Group 1 included patients (n = 10; mean age 39.6 years, mean disease duration 5.6 years) with RA limited to joints (< 6 swollen joints) and without extra-articular manifestations.
- Group 2 included patients (n = 12; mean age 51.4 years, mean disease duration 6.1 years) with advanced joint manifestations (> 6 swollen joints) and with radiologically diagnosed erosions, without subcutaneous nodulosis or extra-articular manifestations.
- Group 3 comprised patients (n = 20; mean age 40.8 years, mean disease duration 6.3 years) with extra-articular manifestations; included 8 patients with nodulosis, 3 with anemia, 6 with secondary Sjogren's, 6 with pulmonary affection, 3 with dryness of eyes, 1 with scleritis, 8 with CAD, overlapping between extra-articular manifestations was observed.

Flow Cytometry

Peripheral blood mononuclear cells were obtained by Ficoll gradient centrifugation. The cells (300,000–500,000) were stained with fluorescein isothiocyanate- (FITC-) conjugated anti-CD4 (MCA1267F) and phycoerythrin- (PE-) conjugated anti-CD28(MCA709PE) monoclonal antibodies (AbD-Serotec-MorphoSys).

Analysis of peripheral blood mononuclear cells was performed using a FACSort flow cytometer (fluorescent-activated cell sorter). The T lymphocytes were excited with 488-nm light from a 15 mW argon ion laser. Logarithmic green and

red fluorescences of FITC and PE were measured through 530/30 nm and 585/42 nm bandpass filters, respectively.

Intact T lymphocytes were identified by their size as assessed by their logarithmic amplification of the FSC and SSC signals. CD4⁺CD28⁻ T lymphocyte regions are selected by plotting CD4 versus CD28.

The number of cells expressing CD4- or CD28-emitting fluorescence signals were multiplied in PMT, then the computer analysed the data and results were expressed as a percentage of cells.

Two-color flow cytometric immunostaining of subjects' peripheral blood showed that bivariate FSC/SSC efficiently distinguished intact T lymphocytes and the mixture of lymphocytes and platelets that scattered within the same FSC/SSC gate. The purity as well as the proportion of T lymphocytes in this gate were identified further using FITC/PE fluorochrome-conjugated monoclonal antibodies to CD4 and CD28.

Then the percentage of circulating T lymphocytes from each group was identified. The fraction of cells within the CD4⁺ population that was CD28⁻ was calculated by gating on the CD4⁺CD28⁺ and CD4⁺CD28⁻ populations.

Statistical Analysis

Computer software package SPSS 13 was used in the analysis for quantitative variables; mean (as a measure of central tendency), standard deviation, and range (as measures of variability) were presented.

The chi square test was used to assess differences between qualitative variables while independent sample t-test and ANOVA (analysis of variances) tests were used for quantitative variables.

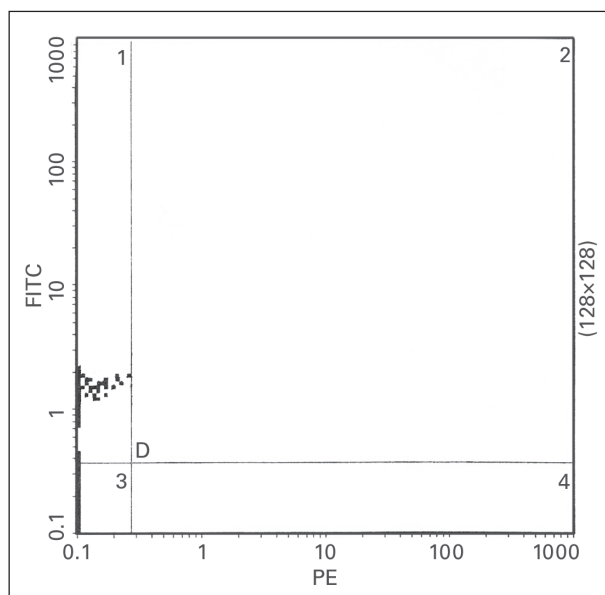
To estimate association between expansion of CD4⁺CD28⁻ T lymphocytes and other variables, Pearson's test was done; correlation coefficient and P value were presented.

For T lymphocytes percentages and all other values among the groups of subjects, the threshold for statistical significance for all comparisons was chosen as p ≤ 0.05.

Table 3. Number and percentage of CD4⁺CD28⁺ and CD4⁺CD28^{null} T lymphocytes between RA patient groups and healthy controls.

	CD4 ⁺ CD28 ⁻ < 15 %			CD4 ⁺ CD28 ⁻ ≥ 15 %		
	n	%	Mean ± SD	n	%	Mean ± SD
Cases	10	23.8	11.12 ± 2.2	32	76.2	36.09 ± 12.2
Controls	8	80	10.5 ± 2.9	2	20	15.6 ± 0.5

Data are expressed as percentage, mean, and standard deviation.

**Figure 1.** Flow cytometry dot plot showing CD4⁺CD28^{null} cells gated on a CD4⁺ T cell population in RA patients.

Results

The results of the present study confirmed that the number of CD4⁺ cells lacking the CD28 molecule was not correlated with age, cholesterol, LDL, HDL, and disease duration in RA patients (Table 1). The frequency of CD4⁺CD28^{null} T cells (Table 2) was significantly higher in RA (group 1: 21.8 ± 3, group 2: 29.6 ± 5.4, group 3: 44.5 ± 9.8) than in control subjects (15.6 ± 0.56) with a significant p value (0.000). RA patients with a percentage of CD4⁺CD28^{null} T cells subset > 15 % (90th percentile of the distribution in the normal population) were defined as having expansion of the

CD4⁺CD28^{null} T cells, the number of RA patients with this expansion is 32 patients (76.19 %; Table 3, Figure 1). Moreover, this study shows that patients with CD4⁺CD28^{null} T cell expansion were characterized by a higher frequency of extra-articular manifestations (44.5 ± 9.8 vs 26.5 ± 6; p = 0.000), and a slight non-significant increase toward a more erosive disease (37.2 ± 12.3 vs 34.8 ± 12.3; p = 0.588, ns). Moreover, incidence of CAD was higher in RA patients with evidence of CD4⁺CD28^{null} cell T cell expansion (47.9 ± 6.7 vs 32.7 ± 11.3; p = 0.000). Patients having negative RF showed more CD4⁺CD28^{null} cell T cell expansion than those with positive RF (39.9 ± 13 vs 30.4 ± 8.5; p = 0.019; Table 4).

Discussion

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease. It is associated with increased mortality, mostly due to an excess of cardiovascular disease. Indeed, the average lifespan of individuals with RA is shortened by 3–18 years. Even after adjustment for traditional cardiovascular risk factors, there is a higher rate of cardiovascular events in subjects with RA than in healthy subjects, which suggests that additional mechanisms are responsible for the excess cardiovascular risk observed in RA [19].

Coronary artery disease (CAD), a manifestation of atherosclerosis, continues to be the most common cause of death in the developed world. Atherosclerosis is predominantly an inflammatory process that involves both the innate and adaptive arms of the immune system [20].

CD4⁺CD28^{null} T cells are expanded in the peripheral blood of patients with unstable angina (UA) and infiltrate unstable coronary plaques, where they undergo clonal expansion, probably triggered by specific antigens [16].

CD4⁺CD28^{null} T cells differ from conventional CD4⁺CD28⁺ helper T lymphocytes in both phenotype and function. CD4⁺CD28^{null} T cells are terminally differentiated and have pro-inflammatory functions characterized by the production of high levels of interferon- γ , tumor necrosis factor- α , and IL-2. In addition, CD4⁺CD28^{null} T cells are cytotoxic and effectively kill endothelial cells in vitro. This is mediated by cytolytic enzymes, such as perforin, granzyme A, and granzyme B expressed by CD4⁺CD28^{null} T cells [6].

Disease-associated expansions of these CD4⁺CD28^{null} T cells have been reported in inflammatory disorders such as rheumatoid arthritis, Wegener's granulomatosis, multiple sclerosis, and ankylosing spondylitis and in chronic infections [21].

Table 4. Clinical characteristics of patients with RA divided by the presence or absence of peripheral blood CD4⁺CD28^{null} T cell expansion.

		CD4 ⁺ CD28 ⁻ < 15 %	p	CD4 ⁺ CD28 ⁻ ≥ 15 %	p
RF	Seronegative	10.8 ± 2.3	0.406	39.9 ± 13	0.019*
	Seropositive	12.4 ± 2.5		30.4 ± 8.5	
ANA	Seronegative	9.4 ± 2.7	0.123	36.6 ± 12.2	0.905
	Seropositive	11.8 ± 1.7		35.9 ± 12.4	
CRP	Negative	11 ± 0.4	0.921	34.2 ± 12.1	0.230
	Positive	11.2 ± 2.7		39.7 ± 12.2	
Bony erosion	Present	11.3 ± 1.7	0.747	37.2 ± 12.3	0.588
	Absent	10.7 ± 3.7		34.8 ± 12.3	
Extra-articular manifestation	Present	10.1 ± 3.2	0.385	44.5 ± 9.8	0.000*
	Absent	11.5 ± 1.8		26.5 ± 6	
CAD	Present	6.5 ± 0.1	0.021*	47.9 ± 6.7	0.000*
	Absent	11.6 ± 1.6		32.7 ± 11.3	

Data are expressed as mean ± standard deviation.

* p < 0.05 means significant result.

One of the best characterized autoimmune diseases associated with increased frequencies of CD4⁺CD28^{null} T cells is rheumatoid arthritis (RA). Expansion of the CD4⁺CD28^{null} T cell subset correlated directly with an increased frequency of extra-articular involvement like rheumatoid vasculitis, and the clinical severity of the disease. These results suggest that the expansion of CD4⁺CD28^{null} T cells does not represent just an epiphenomenon but could have a critical role in the pathogenesis of the disease [5].

The present study aimed to detect the percentage of expansion of CD4⁺CD28^{null} T lymphocytes in the peripheral blood of patients with rheumatoid arthritis which could be a good marker correlating with extra-articular manifestations, CAD, and extent of joint involvement.

In this study, we provided evidence of the presence of circulating CD4⁺CD28^{null} T lymphocytes in rheumatoid arthritis patients as well as normal blood samples; their percentage in the patient groups showed a higher range when compared to the control group. This may be explained by the fact that clonal expansion of CD4⁺CD28^{null} T cells is a characteristic finding in patients with rheumatoid arthritis. Expanded CD4⁺ clonotypes are present in the peripheral blood, infiltrate into the joints, and persist for years. CD4⁺CD28^{null} T cells are oligoclonal lymphocytes that are rare in healthy individuals but are found in high percentages in patients with chronic inflammatory diseases [4].

Also this result coincides with Fasth et al [22], who reported that in the CD4⁺ T cell population the expression of NKR (NK-cell receptors) is primarily found in the CD4⁺CD28^{null} T cell subset. These T cells are frequently found in rheumatoid arthritis.

Among RA patients, the frequency of these CD4⁺CD28^{null} T cell lymphocytes was significantly higher than in controls. Nevertheless, the CD4⁺CD28^{null} T cell compartment differed depending on extra-articular manifestations and joint involvement. The lowest frequency of CD4⁺CD28^{null} T cells was in RA patients with limited joint manifestations. Significantly higher numbers of CD28-lacking lymphocytes were present in patients with extra-articular manifestations, especially patients with CAD. This may be explained by the observation that one of the consequences of dysregulated T cell homeostasis is the emergence of large clonal CD4⁺CD28^{null} T cell populations that are autoreactive and cytotoxic and infiltrate synovial tissue. The highest frequency of CD4⁺CD28^{null} T cells is found in severe RA, particularly in patients with rheumatoid vasculitis. When the inflammatory process in RA spreads to extra-articular sites, such as mid-size arteries and capillaries, morbidity and mortality are clearly increased [23]. In addition, in acute and most severe manifestations of CAD, ie, myocardial infarction and sudden death result from the rupture of a plaque which causes the formation of a thrombus and sudden occlusion of the artery. The presence of activated immune cells, thinning of the fibrous cap, disruption of the collagen matrix, and apoptosis of smooth muscle cells have been implicated in the destabilization of atherosclerotic lesions leading to plaque rupture. Among immune cells, macrophages have a pivotal role in plaque rupture through the release of extracellular matrix-degrading enzymes like metalloproteinase (MMPs). CD4⁺CD28^{null} T cells have been shown to accumulate preferentially in unstable atherosclerotic plaques, therefore being well-located to induce plaque destabilization [24].

Also it was observed that patients with unstable angina (UA) and frequent recurrence of acute coronary events have a median frequency of CD28-lacking CD4⁺ cells about 4× higher than patients with a first-ever acute coronary event during 4 years of clinical observation, and about 9× higher than patients with chronic stable angina (CSA). Moreover,

on multivariate logistic regression analysis, CD4⁺CD28^{null} T cell frequency was an independent predictor of future acute coronary events [16].

Phenotypic and functional properties of CD28-lacking CD4⁺ cells may provide alternative explanations for a possible pathogenic role of this cell subset in favoring CV disease in RA. The expression of CD28 is regulated by a complex cytokine network. T cell activation in the presence of interleukin-12, a proinflammatory cytokine highly expressed in the inflammatory environment of a rheumatoid joint [25, 26], results in the restoration of CD28 gene transcription and cell surface appearance of a functional CD28 molecule on CD4⁺CD28^{null} cells. This may account for the finding that CD4⁺CD28^{null} cells partially regain expression of CD28 in rheumatoid synovium [2]. More interestingly, the up-regulatory action exerted by interleukin-12 on CD28 expression is contrasted by down-modulation induced by another proinflammatory cytokine, TNF- α , which plays a fundamental role in several chronic inflammatory conditions [27]. Thus the description of CD4⁺CD28^{null} T cells in vivo not only during normal aging [28, 29], in which elevated levels of TNF- α have been described [30], but also among patients with inflammatory diseases, including RA [31]. These CD4⁺CD28^{null} T cells have a proinflammatory activity. In particular, they produce large amounts of interferon- γ [32], a typical Th1-cytokine that is involved not only in rheumatoid synovitis but also in atherosclerosis development [15, 26, 33].

Among our RA patients, Hb levels were significantly lower in RA patients with extra-articular manifestations when compared with RA patients with limited joint manifestations and patients with advanced joint involvement.

Anemia is the most common extra-articular manifestation of RA, estimated to occur in 30–60 % of RA patients. There is evidence that patients who are anemic have more severe RA, and also have more affected joints and higher levels of functional disability and pain [34–36].

Both IFN- γ and TNF- α are known for their direct negative effects on erythropoiesis, and TNF- α can shorten erythrocyte half-life because of an increased phagocytosis by macrophages. The presence of an expanded CD4⁺CD28^{null} T cell population with an exceptionally high proinflammatory profile offers a pathogenetic concept for this association. The increased basal TNF- α production of CD4⁺CD28^{null} T cells compared with CD4⁺CD28⁺ cells may explain the effect of these cells on erythropoiesis [37].

This study suggests an association between seronegative RF, ESR, and extra-articular manifestations, especially CAD. Previous studies proved that particularly ESR are significantly associated with the risk of CVD in RA [38], on the other hand, Miguel et al [39] reported that there is no correlation between ESR and intima-media thickness (IMT) of the common carotid artery, an indicator of greater risk of developing cardiovascular events, also other studies showed that elevated RF is associated with CAD [40] opposing our results.

The present study confirmed the association between hypertriglyceridemia and patients suffering from extra-articular manifestations of rheumatoid arthritis.

The changes of lipoproteins during infection and inflammation such as hypertriglyceridemia, elevated triglyceride-rich lipoproteins, the appearance of small dense low-density lipoproteins, increased platelet-activating factor acetylhydrolase activity, and secretory phospholipase A2, sphingolipid-enriched lipoproteins, and decreased high-density lipoprotein (HDL) cholesterol are changes that could promote atherogenesis [41]. Moreover, recently it has been suggested that autoimmune disease contributes to the dyslipidemia process [42].

Conclusion

Elevated plasma ESR and triglycerides are independent risk factors for CAD in patients with rheumatoid arthritis. This finding implies an important relationship between inflammation and atherosclerosis and suggests that autoimmune processes may be involved in the development of CAD in patients with rheumatoid arthritis.

Based on this finding, we suggest that increased CD4⁺CD28^{null} expansion, ESR, and triglyceride levels together with seronegative RF can serve as markers to help identify patients with rheumatoid arthritis who are at risk of developing CAD, hoping that in the future these laboratory parameters could be included in an equation or ratio to predict early the possibility of CAD occurrence so as to prevent it.

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