The Relationship Between Lipid Profile and Inflammatory Markers in Patients with Early Rheumatoid Arthritis.

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Abstract

Rheumatoid arthritis is associated with an excess mortality from cardiovascular disease(CVD) and this may be related to an atherogenic lipid profile. This study was designed to identify whether there was a correlation between disease activity and levels of different lipid fractions in early rheumatoid arthritis (ERA) before used any treatment.

Thirty fife of ERA patients who met in Al-Sader medical city were included in the study compared results with Forty fife apparently healthy individuals. In the present study significant relationship exists between reduced high density lipoprotein –cholesterol (HDLC) and elevated C-reactive protein (CRP) p value was (<0.0001) and elevated erythrocyte sedimentation rate (ESR) p value was (<0.005).Raised of total cholesterol (TC) was associated with raised of both ESR and CRP (<0.0001), (<0.0005) respectively. A significant relationship is demonstrated between elevated ESR and CRP with raised low density lipoprotein –cholesterol (LDLC) ($p<0.0001$) and ($p<0.05$) respectively. Non significant correlation of ESR with raised triglycerides (TG) but significant correlation between CRP and serum TG.

Key words: early rheumatoid arthritis , lipid profile, inflammatory markers.

الخلاصة

الالتهاب المفصلي الروماتويدى المعروف باسم الروماتويد يطلق عليه أيضا الالتهاب المفصلي الرثواني الذي يقترن مع فقدان الحياة إذا ما أصيب المريض بتصلب الشرايين أو الجلطة الناتجة من ترسب الدهون في الأوعية الدموية وانسدادها .

صممت هذه الدراسة للتحقق فيما إذا كانت هناك علاقة بين فعالية المرض ومستويات أشكال الدهون المختلفة لدى مرضى التهاب المفاصل الرثوي في المرحلة المبكرة من المرض قبل ان يتعاطوا أي علاج.تضمنت الدراسة 35 مريض من الذين يراجعون مدينة الصدر الطبية في محافظة النجف الاشرف ,تم مقارنة نتائجهم مع 45 من الأصحاء.

أوضحت الدراسة إن هناك علاقة ارتباطيه معنوية بين انخفاض (HDLC) مع ارتفاع كل من ESR و CRP (<0.005),(<0.0001) على التوالي. يقترن ارتفاع الكوليستيرول الكلي (TC) مع ارتفاع كل من

ESR و CRP (p<0.0001) (p<0.0005), على التوالي كذلك ارتفاع (LDLC) له علاقة بارتفاع كل من ESR و CRP (<.0001), (<0.05)) على التوالي, لوحظ ايضا إن هناك علاقة غير معنوية بين ارتفاع (TG) مع ESR و علاقة ايجابية بين (TG) المصلي و CRP .

مفاتيح البحث: المرحلة المبكرة من مرض التهاب المفاصل الرثوي, صور الدهون, الدلائل الالتهابية.

Introduction

Rheumatoid arthritis is characterized by inflammation and an early rheumatoid arthritis is associated with dyslpidemia ,which may partially explain the enhanced cardiovascular risk. However , it is when this lipidaemia starts[1]. Rheumtoid arthritis causes significant morbidity as a result of synovial inflammation ,joint destruction and associated disability. Several investigators have reported an excess of cardiovascular morbidity and mortality among rheumatoid arthritis patients[2,3]. The inceased prevelance of CVD is probably due to an increase in both the traditional risk factors for atherosclerosis and the presence of chronic inflammation [4]. Traditional risk factor for CVD including atherogenic dyslipidaemia that involved elevation of plasma cholesterol ,tri glycerides or a low/high density lipoprotein that usually results from excessive dietary intake of saturated fat ,cholesterol ,or trans fats[5].Active systemic inflammation has multiple effects which accelerate atherosclerosis . These include changes to the endothelium by c-reactive protein (CRP) and cytokins. Induction of secondary dyslipidaemia ,altered glucose metabolism and creation of a hypercoagulable state due to platelet activation and increased production of clotting factors also play a role [6]. The importance of inflammation in the development of atherosclerosis is supported by the association of cardiovascular death with elevated levels of CRP in patients with inflammatory polyarthritis [7].

In the general The lipid profile includes cholesterol, triglycerides, high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and various risk classifications for coronary heart disease (CHD), cholesterol to HDL ratio, and LDL to HDL ratio.

Cholesterol : Total cholesterol is used to measure lipid status and metabolic disorders. Cholesterol is necessary for life, but is also associated with atherosclerosis. It is used to make hormones, vitamin D, and cell membranes. About two-thirds of the body's cholesterol is made by the liver and one-third obtained through the diet. Increased cholesterol is found in high fat diets, primary hypercholesterolemia, the nephritic syndrome, hypothyroidism, primary biliary cirrhosis and in some cases of diabetes. Low levels have been found in malnutrition, malabsorption, severe liver disease, polycythemia vera, etc. The method is by spectrophotometry. Normal values are based on age. The "normal or reference ranges" has been lowered in recent years to combat the rapid increase in heart disease. In people under 19 years of age, the normal value is less than 170 mg/dL. In people over 19 years of age, the normal value is less than 200 mg/dL.

Triglycerides : Like cholesterol, triglycerides (TG) are used to measure lipid status and metabolic disorders. A patient must absolutely be fasting for an accurate measurement. Triglycerides are the major component of chylomicrons and VLDL, two types of lipoproteins. They may be elevated in hypothyroidism, diabetes, chronic

liver and kidney diseases, pancreatitis, some genetic types of hyperlipidemia, alcohol abuse, estrogen (pregnancy or oral contraceptive pills), and certain medications (thiazide diuretics). The triglyceride level is used to calculate the LDL, however, to get a correct answer, the TG must be 400 mg/dL or less. A turbid serum specimen indicates a TG level of around 400 mg/dL. The method is by spectrophotometry. (< 150 mg/dl is normal, 150 – 199 mg/dl is borderline-high, 200 – 499 mg/dl is high and > 500 mg/dl is very high).

HDL (High-Density Lipoprotein): HDL is called the "good cholesterol". It tends to carry cholesterol away from tissues. All other risk factors considered, a high HDL is a good risk factor. The method is by spectrophotometry (< 40 mg/dl is low and > 60 mg/dl is high).

LDL (Low-Density Lipoprotein)-Calculated: LDL cholesterol is called the "bad cholesterol". It is part of the lipid profile and is one of the more important "risk factors" for atherosclerotic (CHD) disease. LDL is the cholesterol component that binds to liver receptors and tends to control the formation of cholesterol. The method is by calculation using the Friedewald formula. The formula can only be used when the TG are less than 400 mg/dL. LDL core lipids contains about 10% TG and ``145% cholesterol.(< 100 mg/dl is optimal, 100 – 129 mg/dl is near optimal, 130 – 159 mg/dl is borderline high, 160 – 189 mg/dl is high and > 190 mg/dl is very high).

Very Low Density Lipoprotein (VLDL): VLDL is a type of lipoprotein and helps carry triglycerides to the liver and other parts of the body. Density refers to the amount of lipids per lipoprotein versus proteins. Core lipids in chylomicrons contain about 85% triglycerides and 5% cholesterol, VLDL contains about 60% TG and 15% cholesterol. Elevated VLDL levels are found in Type IV hyperlipidemias.

Cholesterol to HDL Ratio: The Cholesterol to HDL ratio is a calculation of your risk for heart disease. It is optimal to have a low ratio. A low ratio indicates that total cholesterol is comprised mostly of HDL particles. This ratio is considered the most important indicator for atherosclerosis. Average risk for male (5.5-9.6) and for female (4.5-7.1) respectively.

LDL to HDL Ratio: The LDL to HDL ratio is also a heart disease risk indicator. It is best to have a low ratio as this indicates there is sufficient HDL in relation to LDL to aid in prevention of atherosclerosis. Excessively high or low levels can indicate a problem. It is best to maintain these in proper balance to HDL. Average risk for male (3.7-6.3) and for female (3.3-5.0) [8,9,10].

Many previous works showing that rheumatoid arthritis is associated with an adverse lipid profile [11] ,RA likely influences lipoprotein metabolism leading to quantitative and qualitative alterations of low density lipoproteins, Glucocorticoids alter carbohydrate and lipid metabolism. However, by reducing the inflammation level, the net effect on lipid parameters and on the CV risk may be favorable[12]. Data from open follow-up studies would suggest that disease modifying therapy use is associated with a beneficial effect on lipid parameters and with a reduction in the incidence of CV disease[13].

Materials and Methods

Totally 80 subjects were enrolled in the study , 35 [25female, 10 male; mean of age (43.67±10.2) years] patients with early rheumatoid arthritis (ERA) and had early inflammatory disease (disease duration >12 months) before use any type of drug that

disease modifying anti rheumatic drug(DMARD), 45 healthy individuals (mean of ages 38.85±9.65) years . All patients were recruited from the out patients rheumatology clinic of the AL-Sader medical city in Najaf government. Disease activty was assessed by that patient had a minimum of three articulators involved, at least 9 sites of painful tenderness on digital compression , and had a morning rigidity exceeding 45 minutes and an ESR (erythrocyte sedimentation rate over 28 mm/hours[14].Overnight fasting blood samples were drawn from rheumatoid arthritis patients and allowed to clot , then centrifuged for 15 min at a speed of 250 xg . Sera were separated to determine lipid profile ,including total cholesterol (TC),triglyceride (TG), high density lipoprotein cholesterol (HDLC) and low density lipoprotein cholesterol (LDLC) . Standard hematological and biochemical procedures were used TC,TG,HDLC and LDLC of all subjects were evaluated using commercial analytical kits from BIOLABO SA (02160 Miazy France).ESR estimation was performed by westergen technique in each patients . Levels of c-reactive protein CRP determent by enzyme immunoassay [15] (Virgo c-reactive protein 150 kit ;Hemagen, Waltham, Massachusette,USA)

Result and Discussion

The result of analysis were confirmed by students *t* test and linear regression analysis was used to evaluate the correlation among parameters .All results were expressed as mean values ±SD ; statistical significance was defined as $p<0.001$ and $p<0.005$. There was no observed differences in six distribution and age between early rheumatoid arthritis (ERA) and controls . ERA patients exhibited increased levels of inflammatory markers that involved c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) when compared with controls ($p<0.001$) ,as well as ERA patients exhibited a mild dyslipidemia characterized by an increase in the serum levels of total cholesterol (TC), low density lipoprotein cholesterol(LDLC) and tri glycerides as well as by decrease in the serum levels of high density lipoprotein cholesterol (HDLC) as shown in table (1). Expressed as percentages of the calculated mean of the controls ,we found that the total cholesterol levels in patients were on average 4.3% higher ,tri glyceride levels were 17.2% higher and high density lipoprotein cholesterol levels were 8.8% lower. Association between inflammatory markers and different lipid fractions were assessed using the linear regression analysis and the p value obtained are shown in table (2).

Table (1): Inflammatory markers and lipid profile of early rheumatoid arthritis (ERA) compare with healthy individuals .

Parameters	Groups	Rang	Mean ± SD	P value
CRP mg/dl	Patients	7-104	3±0.32	<0.001
	Controls	1-5	45.52±9.5	
ESR mm/h	Patients	20-110	5.2±3.1	<0.001
	Controls	2.4-14.6	52±19.7	
Cholesterol mg/dl	Patients	205-280	230±50.3	<0.001
	Controls	90-220	192.4±33.3	
HDL mg/dl	Patients	30-55	37.5±11.8	<0.005
	Controls	45-68	51.4±10.2	
LDL mg/dl	Patients	130-192	160.6±42.3	<0.005
	Controls	100-145	125.5±30.3	
VLDL mg/dl	Patients	81.3-210	165.5±14.7	<0.005
	Controls	45.2-82	58.3±9.5	
TG mg/dl	Patients	160-420	205±28	<0.001
	Controls	90-160	105.5±19	
TC/HDL ratio	Patients	4.5-18	9.7±4.4	<0.005
	Controls	0.99-3.2	2.1±0.78	
LDL/HDL ratio	Patients	1.5-7.5	5±1.3	<0.001
	Controls	0.66-1.2	0.75±0.23	

Table (2):Results of unvaried analysis of inflammatory markers and lipid fractions of patients with early rheumatoid arthritis (ERA).

Lipid fractions	ESR mm/h	P value	CRP mg/dl	P value
TC mg/dl	0.67	<0.0001	0.58	<0.0005
LDLC mg/dl	0.65	<0.0001	0.3	<0.05
HDLC mg/dl	0.41	<0.005	0.7	<0.0001
TG mg/dl	0.26	N.S	0.31	<0.05

A statistically significant relationship is demonstrated between elevated ESR and CRP with raised LDLC ($p<0.0001$) and ($p<0.05$) respectively. Reduced levels of HDLC was associated with raised ESR and CRP($p<0.005$) and ($p<0.0001$) respectively. While strong positive correlation of ESR and CRP with increase in serum levels of total cholesterol TC ($P<0.0001$) and ($P<0.0005$) respectively . Non significant correlation of ESR with raised tri glycerides (TG) but significant correlation between CRP and serum TG.

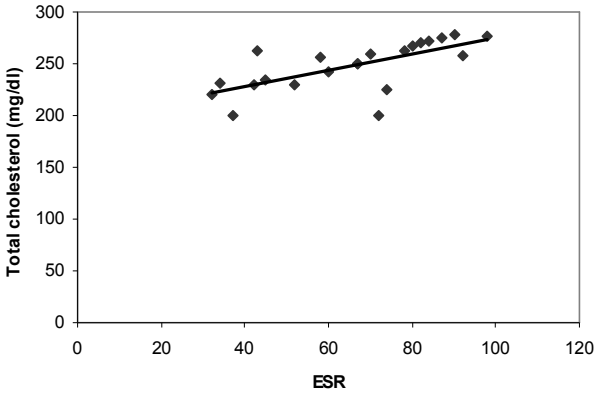


Fig (1) :correlation between serum levels of total cholesterol and erythrocyte sedmentation rate(ESR).

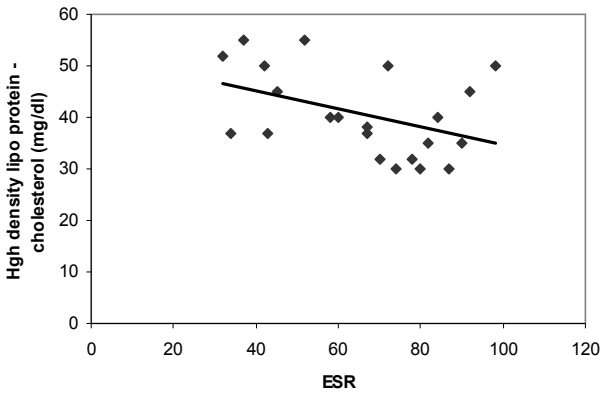


Fig (2): Correlation between serum levels of high density lipoprptien-cholesterol and erythrocyte sedmentation rate (ESR).

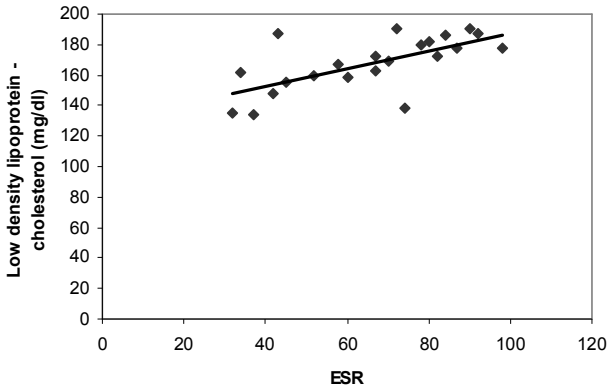


Fig (3): Correlation between serum levels of low density lipoprotein -cholesterol and erythrocyte sedmentation rate (ESR).

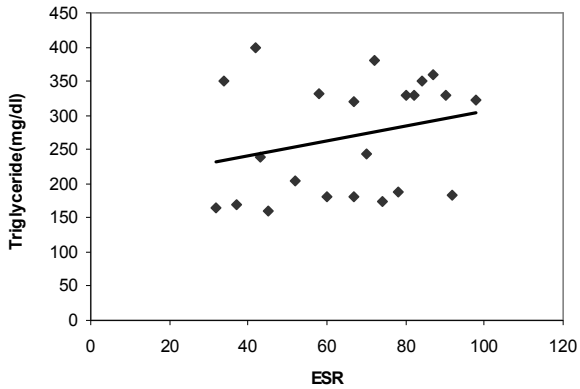


Fig (4): Correlation between serum levels of triglycerides and erythrocyte sedmentation rate (ESR).

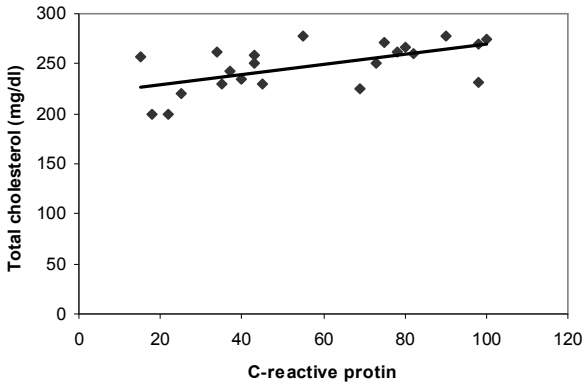
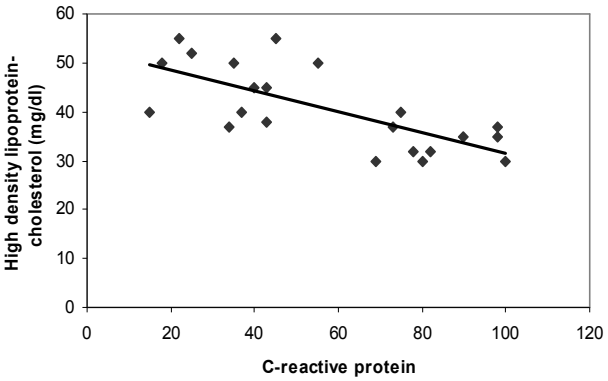
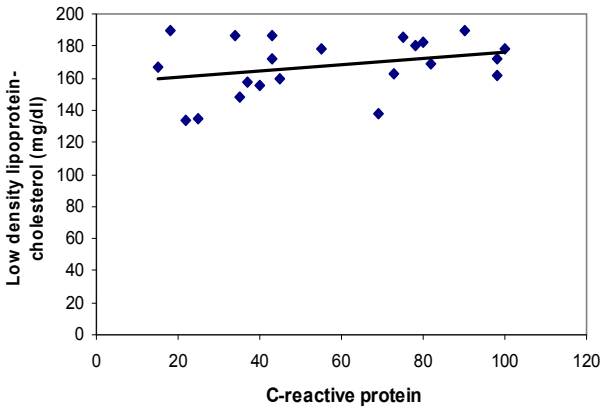


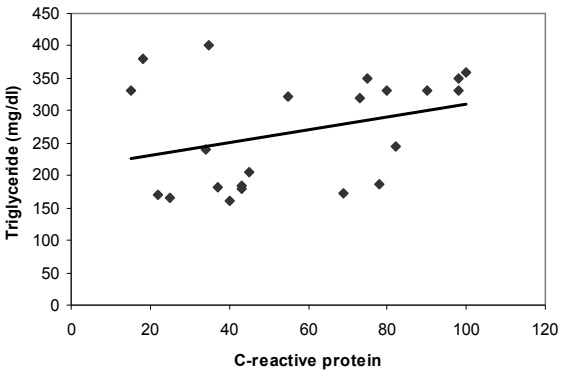
Fig (5):correlation between serum levels of total cholesterol and C-reactive protien CRP



Fig(6): correlation between serum levels of high density lipoprptein - cholesterol and C-reactive protein CRP



Fig(7): Correlation between low density lipoprotein-cholesterol and C-reactive protein CRP



Fig(8):Correlation between serum levels of triglycerides and C-reactive protein CRP

Results of the current investigation were agreed with the findings of some published articles (1,11). They have also found approximately same the relation ship between abnormalities changes of lipid pattern and inflammatory markers.

Our study shows that the lipid profile of blood donors who later developed rheumatoid arthritis is more atherogenic than that of matched controls. This lipid profile is characterised by higher total cholesterol, triglyceride and lower HDLc levels. Even after adjusting for CRP levels, the lipid profile remained more atherogenic in patients.The differences in the various lipid values are small but may have clinical relevance, in the light of results from other studies [16–18].

Contrary to the expectations, CRP had only a marginal influence on the differences in lipid levels between patients and controls. Erythrocyte sedmentation rate ESR, showed a comparable, marginal influence on the differences in lipids between patients and controls. The influence of CRP on lipid levels was more for patients group—that is, increase in of CRP level was associated with a decrease HDLc, and with an increase in total cholesterol,LDLc and triglycerides resulting in a higher atherogenic index (ie, ratio of total cholesterol to HDLc).

Growing evidence indicates that inflammation has an important role in the pathogenesis of cardiovascular disease, particularly in atherosclerosis[19]. In addition to a postulated direct effect of inflammation on endothelial cells, there is mounting evidence that inflammation can also increase the cardiovascular risk by deterioration of the lipid profile. This is supported by the demonstration of a decrease in HDLc levels and an increase in triglycerides and during an acute-phase response [20]. Other investigators found an association between increase in lipids as oxidised low-density lipoprotein cholesterol and proinflammatory cytokines as CRP, interleukin 6 and tumour necrosis factor a [21]. Our findings confirm these effects of inflammation on the various lipid concentrations. As the changes in CRP only explained a small part of the observed differences in lipid levels that remained after adjusting for CRP, an alternative explanation is required.

Two possible explanations are plausible. Firstly, in view of the association between the development of rheumatoid arthritis and a less favourable lipid profile, a (marginally) deteriorated lipid profile may render a person more susceptible to inflammation or inflammatory diseases. In other words, one or more of the examined lipids could have a regulatory effect on inflammation. Several reports show anti-inflammatory effects of HDLc and particularly apo AI. It is suggested that apo AI is able to inhibit interactions between T lymphocytes and monocytes, thereby modulating the inflammatory response [22]. Moreover, another study showed the ability of apo AI to inhibit interleukin 1 and tumour necrosis factor a, which further supports the theory of an active modulating role of lipids in inflammation [23].

Secondly, a less favourable lipid profile is related to the development of rheumatoid arthritis by a common or linked background. This could be a socioeconomic (including dietary) or genetic background. A few studies have indicated a genetic predisposition for dyslipidaemia in patients with rheumatoid arthritis[24]. Further unraveling of the human genome will probably elucidate this predisposition. Further investigations into genetic markers that could single out the

population at risk should be undertaken.

In summary, our study supports the observation that patients with rheumatoid arthritis have a more atherogenic lipid profile even in the preclinical phase of rheumatoid arthritis, which ultimately could explain the increased cardiovascular risk in patients with rheumatoid arthritis. Furthermore, we show that inflammation is associated with a (further) deterioration of the lipid profile. However, contrary to expectations, inflammation can explain only a small part of the observed differences in lipids between people who later develop rheumatoid arthritis and controls. Whether lipids modulate the susceptibility to the development of inflammatory diseases such as rheumatoid arthritis remains to be elucidated.

References

1.Van Halm VP, Nielen MJ,et al.: ***Arthritis rheum*** , 2007, **66(2)**, 184-188.

2. Gabriel SE, Crowson CS, Kremers HM, Doran MF, et al : ***Arthritis Rheum*** , 2003, **48**, 54-58.

3. Symmons DP: ***Rheumatology***,2005, **44**, iv14-iv17.

4- Satter N, Carey DW, et al : Explaining how high –grade systemic inflammation accelerates vascular risk in rheumatoid arthritis., 2003, **108**, 2957-63.

5- HY, Chen DY, Lan JL, Chiang EP: ***Int J Epidemoiol***, 2007, **36**, 666-76.

6. .Vanleuven SI, Franssen R, Kastelein JJ,et al, ***Rheumatology***, 2008, **47**, 3-7.

7.Goodson NJ, Symmons DP, Scott DG et al: ***arthritis Rheum***, 2005, **52**, 2293-9.

8. Report of the National Cholesterol Treatment Program Expert Panel on Detection, ***Arch Intern Med***, 1998, **148**, 36-9.

9.Vance, D.E., Vance, J.E. Biochemistry of Lipids, Lipoproteins, and Membranes. New York, Elsevier Science, 1996.

10.Vanleuven SI, Franssen R, Kastelein JJ,et al.NIH publication No.01-3305,***JAMA***, May2001, **285**, 2486-97.

11. Douglas W, Sayed F, Alan D: ***Newzeland Med jour***, 2006, 2006, **119(1240),** 1-4.

12. Hansel B, Bruckert E: Lipid profile and cardiovascular risk in patients with rheumatoid arthritis :effect of the disease and of drug therapy) Service d'endocrinologie-métabolisme et de prévention cardiovasculaire, ***hôpital de la Pitié-Salpêtrière,*** 2008, 47-83, boulevard de l'Hôpital, 75013 Paris, France.

13.Sara I, Alexandra N, Janis B, et al: ***Oxford Jour, Med, Rheum***, 2011, **49(Issu2)**, 295-307.

14.Scott DL: ***Arthritis and rheumatism,*** 1994, **10**, 1506.

15.Chiang EP, Bagley pj, Selhub j, et al., ***Am J Med,*** 2009, **114**, 283-287.

16. Menotti A, Lanti M., ***Heart***, 2006, **89**, 19–24.

17. Menotti A, Kromhout D, Blackburn H, Jacobs D, Lanti M. ***Eur J Epidemiol*** , 2004, **19**, 417–24.

18. Sprecher DL, Watkins TR, Behar S, Brown WV, Rubins HB, Schaefer EJ., ***Am J Cardiol***, 2009, **91**, 575–80.

19. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al., ***N Engl J Med***; 1999, **341**, 410–18.

20. Cabana VG, Siegel JN, Sabesin SM. ***J Lipid Res***, 2010, **30**, 39–49.

21. Hulthe J, Fagerberg B., ***Arterioscler Thromb Vasc Biol***, 2002, **22**, 1162–7.

22. Burger D, ***Autoimmun Rev***; 2007, **1**, 111–17.

23. Hyka N, Dayer JM, Modoux C, Kohno T, Edwards CK III, Roux-Lombard P, et al. ***Blood***; 2001, **97**, 2381–9.

24. Tanimoto N, Kumon Y, Suehiro T, Ohkubo S, Ikeda Y, Nishiya K, et al. ***Life Sci*** ; 2003, **72**, 2877–85.