Original Article

IL-1β level in Sudanese patients with atherosclerotic coronary heart disease

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ABSTRACT

Background: High level of interleukin-1β (IL-1β) is common in patients with coronary heart disease (CHD). However, the effects of age and ethnicity on IL- 1β levels are not clear. **Aim:** This study assessed IL-1β level in Sudanese patients with CHD and evaluated the effect of age on systemic level of IL-1β. **Methods and materials:** The study involved a control group of eighty-one apparently healthy subjects and a test group of one hundred patients with atherosclerotic CHD proved by coronary angiography. Patients' glycaemic control, lipid profile and the levels of IL-1β were assessed using appropriate laboratory tests. Patients with CHD were classified according to their ages into < 40, 40-49, 50-59 and ≥ 60 years old. **Results:** Age correlates negatively with IL-1β level (correlation coefficient = - 0.324, P = 0.000). The mean level of IL- 1β in patients with atherosclerotic CHD (M±SD = 7.05±27.18 pg/ml) was significantly lower compared with the control group (M±SD = 9.86±7.41 pg/ml). The mean level of IL-1β in atherosclerotic patients with CHD less than 40 years old (M±SD = 48.52±85.59pg/ml) was significantly higher (P = 0.005) compared with the control group (M±SD = 11.17±5.65 pg/ml). In contrast, the means of IL-1β in patients with atherosclerotic CHD among subjects ≥ 40 years old and in all age classes were significantly lower compared with the control group (P < 0.05). **Conclusion:** Alteration in IL-1 β levels among atherosclerotic patients with CHD is age-dependent; increasing in those < 40 years and declining in those ≥ 40 years.

Key words: Age, atherosclerosis, interleukin-1β, coronary heart disease.

INTRODUCTION

Nowadays, there are growing evidences that relate much of the cardiovascular disorders to the disturbed immune responses.[1] For example, the current understanding for the pathogenesis of atherosclerosis is largely based on the imbalance between different inflammatory mediators.[2-4] Interlukin-1 (IL-1) is the chief regulator of many inflammatory responses and is involved in many autoimmune diseases including coronary atherosclerosis.[1]

IL-1 is actually two separate proteins, interleukin-1α (IL-1α) and interleukin-1β (IL-1β). High levels of IL-1β is a common finding in most previous studies investigating inflammatory cytokines in atherosclerotic patients with coronary heart disease (CHD).[2,5-7] However, systemic level of IL-1β may still be unreliable marker for atherosclerosis. This is because systemic level of IL-1β could not faithfully reflect the local inflammatory process near the atheromatous lesions.[2] Moreover, level of IL-1β is proved to be modified by cholesterol lowering drugs,[6,8,9] aging[10] and

ethnic factors.[11,12] This in turn may add to the expected variation in IL-1β level among CHD patients as well as healthy subjects.

In Sudan, studies IL-1β in atherosclerotic patients with CHD are scarce, if ever. However, comparable studies in American blacks suggest lower level of IL-1β[11] and increased IL-1 receptor antagonist (IL-1 Ra)[12] when compared with white Americans. This study aimed to evaluate IL-1β level in Sudanese patients with coronary heart disease. The effect of age on systemic level of IL-1β was also examined.

MATERIALS AND METHODS

Subject selection
The study received ethical clearance from the ethical review committee at the Faculty of Medicine and Health Sciences, Alneelain University, Khartoum, Sudan. The authorities of the chosen hospitals were informed and their permissions were taken accordingly.

The study involved two groups: a control group of eighty-one apparently healthy subjects, 55 (67.9%) were male, and a test group of one hundred atherosclerotic patients with CHD, 57 (57.0%) were male, proved by coronary angiography. Patients were recruited mainly from catheterization centers of Khartoum state, Sudan while healthy volunteers were recruited from hospital employees. All control subjects with hypertension, diabetes mellitus, hyperlipidaemia or other known risk factos for atherosclerosis were excluded from the study. The age of both groups ranged between 18-84 years. Following history taking and clinical examination, blood samples were taken to assess patients' glycaemic control, lipid profile and the levels of IL-1β. Mean arterial blood pressure (MABP) for each subject was determined by the formula:
MABP = diastolic blood pressure + [(systolic blood pressure – diastolic blood pressure)/3].

Body mass index (BMI) was determined using the formula: BMI (Kg/m^2) = Weight (Kg) / (Height (m))^2. Atherosclerotic patients with CHD were classified according to their ages into < 40 (8%), 40-49(13%), 50-59 (39%) and ≥ 60 (40%) years old.

Statistical analysis
Statistical evaluation was performed using the SPSS (SPSS for windows version 19) and Microsoft Office Excel (Microsoft Office Excel for windows; 2007). Normal distribution of studied variables was examined using Kolmogorov-Smirnova and Shapiro-Wilk tests. Unpaired T-test and Mann-Whitney U test were used to assess significant difference in the means of the studied variables in the different groups. *P*<0.05 was considered significant.

RESULTS

The mean±standard deviation (M±SD) of age was 44.42±10.36 years in the control subjects and 56.13±11.99 years in atherosclerotic patients with CHD. Age correlates negatively with IL-1β level (correlation coefficient (CC) = -0.324, *P* = 0.000). The characteristics of the control and test groups are given in table 1. The mean level of IL-1β in atherosclerotic patients with CHD (M±SD = 7.05±27.18 pg/ml) was significantly lower compared with the control group (M±SD = 9.86±7.41 pg/ml) (figure 1). When age was considered, the mean level of IL-1β in atherosclerotic patients with CHD (M±SD = 48.52±85.59pg/ml) was significantly higher compared with the control group (M±SD = 11.17±5.65 pg/ml) in those less than 40 years old (*P* = 0.005). In contrast, the means of IL-1β in atherosclerotic patients with CHD were significantly lower compared with the control group in all age classes ≥ 40 years old (*P* < 0.05) (table 2). Figure 2 shows the comparison for IL-1β levels in different age groups.

DISCUSSION

The novel finding of this study is the significantly lower level of IL-1β among atherosclerotic patients with CHD when compared with the control group. However, previous studies investigating inflammatory cytokines in patients with CHD repeatedly revealed higher concentration of IL-1β,[2,5-7] especially in early phases of the disease.[5] IL-1β gene expression was proved to be enhanced in patients CHD,[6] highlighting the important role of IL-1β in the pathogenesis of coronary atherosclerosis. Experimental animal showed that chronic treatment with interleukin-1β led to coronary intimal lesions and vasospastic responses.[13] Alternatively, significant decrease in the severity of

atherosclerosis occurred in those lacking IL-1β.[14] This finding was further supported by a recent study which demonstrates that an antibody against IL-1β can slow down the progression of atherosclerosis in vivo, adding further support for the importance of this cytokine in the development of atherosclerosis.[3]

It is worth mentioning that in spite of the fundamental role of IL-1β in the pathogenesis of coronary atherosclerosis, some studies failed to demonstrate significant difference in the concentration of this cytokine when patients with CHD were compared with the controls.[16] It has been accepted, although not confirmed by experimental studies, that inflammatory biomarkers associated with atherosclerosis of the coronary arteries are released from unstable plaques. This could explain why systemic level of IL-1β could not reliably reflect the local inflammatory status near the atherosclerosis plaque locations.[2] Alternatively, a recent study did not find any difference between intracoronary and systemic levels of any inflammatory marker in patients with acute coronary syndrome, patients with stable angina or in the control group.[4] The same study observed that excess circulating inflammatory markers are released from non-coronary sources.

Table 1: Characteristics of the control and test groups

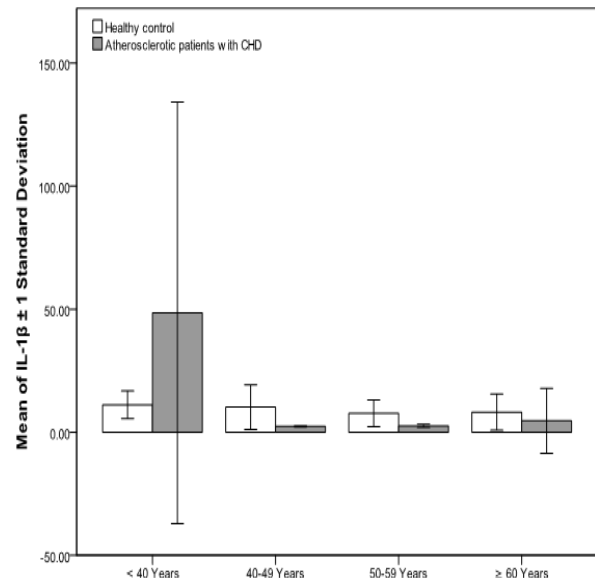|	Control Group (N = 81)	Athero-sclerotic Patients with CHD (N = 100)	*P* Value
	(M±SD)	(M±SD)	
Age (years)	44.42±10.36	56.13±11.99	0.000*
Weight (Kg)	72.68±18.02	77.83±15.25	0.042*
Height (Cm)	170.33±13.64	164.48±14.02	0.000*
Body Mass Index	26.63±20.51	29.60±11.44	0.000*
Systolic Blood Pressure	120.37±7.15	134.84±22.29	0.000*
Diastolic Blood Pressure	78.79±5.23	80.87±11.35	0.094
Mean Arterial Blood Pressure	92.65±5.21	98.86±13.14	0.000*
Random Blood Glucose Level (mg/dl)	86.58±3.92	146.75±65.72	0.000*
Triglyceride Level (mg/dl)	93.09±30.69	93.60±43.36	0.659
Cholesterol Level (mg/dl)	140.39±24.54	145.43±33.51	0.438
HDL Level (mg/dl)	33.86±6.52	25.82±4.55	0.000*
LDL Level (mg/dl)	87.91±25.12	100.88±35.50	0.005*
HDL/LDL	0.43±0.18	0.31±0.28	0.000*

Table 2: Comparison between IL-1 β levels in different age groups

Age	IL-1β Level in the Control Group (pg/ml)	IL-1β Level in the Athero-sclerotic Patients with CHD (pg/ml)	*P* Value
	(M±SD)	(M±SD)	
< 40 Years	11.17±5.65	48.52±85.59	0.005*
40-49 Years	10.21±9.02	2.36±0.20	0.026*
50-59 Years	7.74±5.41	2.58±0.63	0.000*
≥ 60 Years	8.17±7.39	4.65±13.21	0.046*
All Ages	9.86±7.41	7.05±27.18	0.000*
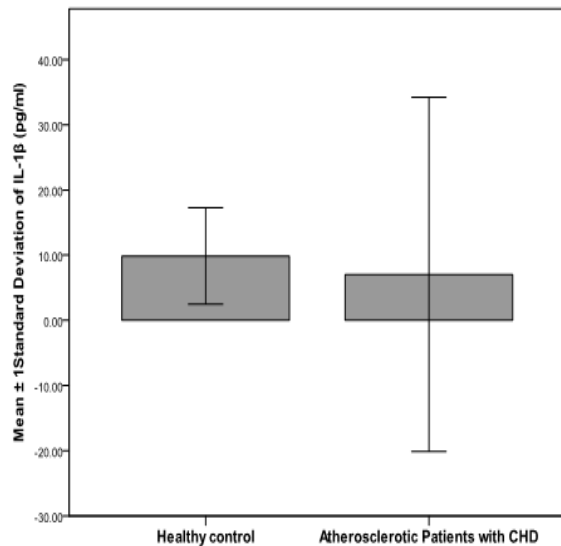
Figure 1: Means and standard deviations of IL-1 β in the test and the control groups

Figure 2: Means and standard deviations of IL-1 β in different age groups

It is evident from above reports that all previous studies agreed that IL-1β level is either significantly higher or not different in patients with CHD compared with the healthy subjects. The present study is the first that demonstrated significantly lower level of IL-1β among patients with atherosclerotic CHD; disputing the current understanding of the pathogenesis of coronary atherosclerosis.

Although old studies failed to demonstrate significant increase in the levels of IL-1β among elderly compared with younger ladies,[16,17] a very recent study showed that early production of IL-1β may decline with age.[10] The later finding is further supported by the results of the current study which showed significant negative correlation between age and IL-1β level. Moreover, the present results also demonstrated that the mean age of

atherosclerotic patients with CHD was significantly higher compared with the control group. Thus, the significantly lower IL-1β level in patients with atherosclerotic CHD could be secondary to advanced age. Another important outcome of the current data is that the IL-1β levels were higher in patients with atherosclerotic CHD who are less than 40 years old. The reverse is true for elder atherosclerotic patients whose IL-1β levels were usually below the control group. This finding further support the implications of Ozeren *et al.*[5] and others[18] that reported that IL-1β level tends to be higher in the early phases of CHD.

Statins treatment was proved to inhibit the expression of IL-1β on both the mRNA and protein levels.[6,8,9] Actually, the current results showed no statistical difference in the means of cholesterol and triglyceride levels when patients with atherosclerotic CHD were compared with the control group. Atherosclerotic patients with CHD routinely received statins therapy, among the other treatment, and are expected to lower their IL-1β levels through above-mentioned mechanisms.

Ethnic variation in the concentration of circulating inflammatory biomarkers, possibly due to demographic, lifestyle or genetic factors, was well documented in the literature.[11,12,19,20] For example, the IL-1β TaqI(-) allele was significantly more frequent in white patients with inflammatory bowel diseases compared with the black patients.[11] In contrast, the 410-bp allele of the IL-1 Ra was significantly increased in black as compared to white subjects.[12] Therefore it is essential to know the normal range as well as the major determinants of inflammatory biomarkers in different ethnic groups before being used for the purposes of diagnosis and/or prognosis.

CONCLUSION

It is evident that the pattern of rise in IL-1β levels among atherosclerotic patients with atherosclerotic CHD is determined by age; increasing in those < 40 years and declining in those ≥ 40 years. In contrast, it can decrease in elderly CHD patients. Aging, statins therapy and ethnic variations may elucidate the differences in IL-1β levels among different age classes; however, further researches are desirable to explore the possible grounds, and

probably the consequences, for this novel finding.

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