

Associations of Interleukin-6 Levels and Lipid Profiles in Women with Coronary Artery Disease: A Comparative Study across Menopausal and Reproductive Stages at RSUP. H. Adam Malik

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ABSTRACT

Aims and background: Menopause alters the lipid profile by raising total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL C), and very low-density lipoprotein cholesterol (VLDL C) while lowering high-density lipoprotein cholesterol (HDL C). In women with cardiovascular risk linked to interleukin-6 (IL-6) and C-reactive protein (CRP) plasma levels, this study aimed to examine the connection between IL-6 levels and lipid profiles in both menopausal and reproductive women with coronary artery disease (CAD). Age, body mass index (BMI), smoking history, blood pressure, alcohol consumption, diabetes, and exercise frequency were found to be related to IL-6 concentrations.

Materials and methods: Observational analytical study with a case-control design was used in this study. Two groups (menopausal and reproductive women) of 44 women had their IL-6 levels and lipid profile checked. The data were then analyzed using a correlation test.

Results: The BMI, smoking behaviors, and family history of heart disease were observed to significantly differ between the menopausal and reproductive groups of women ($p < 0.05$). In both groups, there was a substantial relationship ($p < 0.05$) between IL-6 levels and lipid markers such as TC, LDL, and TG. The HDL levels did not differ statistically significantly ($p > 0.05$) between the two groups, however. The length of menopause and IL-6 levels were significantly correlated in the group of menopausal women ($p < 0.05$).

Conclusion: The lipid profile (total cholesterol, LDL, and triglycerides) and IL-6 levels were significantly correlated in menopausal women and reproductive women with CAD.

Clinical significance: Elevated IL-6 is associated with disturbance of lipid profile among both menopausal and reproductive women with CAD.

Keywords: Coronary artery disease, Interleukins-6, Lipid profile, Menopause.

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INTRODUCTION

Menopause is defined as 12 months of amenorrhea or cessation of menstruation without any other cause. During menopause, there is a decline in ovarian function which causes decline in estrogen production. This causes physiological changes which result in a decrease in various bodily functions and quality of life, including cardiovascular disorders.¹

Based on demographic data, every year 25 million women worldwide experience menopause. By 2030, 1.2 billion postmenopausal women are expected to exist globally.¹ The age of menopause for women in developed countries such as the United States and England is 51.4 years, while in Southeast Asian countries is 51 years. The menopause age for Indonesian women is 50 years. Given the 70-year life expectancy of Indonesian women, it will take about 20 years for them to encounter a range of health issues related to menopause.^{1,2}

Many issues are linked to menopause, such as weight gain, diminished cognitive function, genitourinary dysfunction, hot flashes, sleep issues, mental disorders, and sexual dysfunction. An issue associated with menopause is the increased prevalence of cardiovascular disease.²⁻⁴ Hormone-responsive tissues, including the brain, bones, and cardiovascular system, are more susceptible to disease during menopause. Researchers from Framingham

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discovered that 10 years following menopause, the incidence of cardiovascular disease increased fourfold. However, the aging process is a confounding variable in this case. Menopause is also associated with weight redistribution and weight gain in majority of women. Obesity and weight gain raise postmenopausal women's risk of metabolic problems. Menopause can be considered as a predictor of metabolic syndrome independent of age.³⁻⁵

The common occurrence of menopause-induced alterations in proinflammatory cytokine activity is beginning to emerge, and it may have a major effect on the functionality of all tissues. Several years back, it was discovered that in the absence of estrogen, *ex vivo* cultures of circulating monocytes would naturally produce more proinflammatory cytokines, namely interleukins-1 (IL-1), interleukins-6 (IL-6), and tumor necrosis factor- α (TNF- α).⁶⁻⁸ Estrogen deficiency has also been shown to increase cells responding to some of these cytokines by increasing the number of cytokine receptors and cytokine action cofactors, thus strengthening the increasing effect of cytokines.^{8,9}

Increases in lipoprotein (a) [Lp(a)], total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) are linked to menopause. While it still tends to be higher in women than in men, high-density lipoprotein cholesterol (HDL-C) tends to decrease after menopause. The levels of IL-6 and C-reactive protein (CRP) in the blood of women who are reproductive are linked to risk factors such as age, body mass index (BMI), smoking, blood pressure, alcohol, diabetes, and physical activity. By stimulating these risk factors, atheromatous plaques' smooth muscle cells and macrophages may release more IL-6, which raises the likelihood of coronary artery disease (CAD).^{8,9}

MATERIALS AND METHODS

This research is an analytical observational study with a case-control design which aims to determine the correlation between IL-6 levels and lipid profiles in women of menopausal and reproductive age who suffer from CAD. The research was carried out at the Cardiology Department/SMF Polyclinic at H. Adam Malik Hospital with measurements of IL-6 levels and lipid profiles carried out at the Prodia Medan Clinical Laboratory. The time span of this research is from 22 August to 13 October 2023. This research has received approval from the Health Research Ethics Committee of the Universitas Sumatera Utara, 21 August 2023, No.893/KEPK/USU/2023.

Research Population

The population of this study were all women who had a history of CAD who came to the Cardiology Department/SMF Polyclinic at RSUP H. Adam Malik Medan. The subjects in this study were women who had a history of CAD who visited cardiology clinic at RSUP. H. Adam Malik and met the inclusion and exclusion criteria. Based on the sample size calculation used, the number of subjects for this research was 22 research subjects for each group (Table 1).

Table 1: Demographic characteristics of research subjects

Characteristics	Woman menopause age	Woman reproductive age	<i>p</i>
Age (years)			
Mean (SD)	58.86 (7.30)	42.23 (4.41)	–
Median (Min–Max)	56 (52–81)	41.5 (36–48)	
BMI (kg/m ²)			
Mean (SD)	31.55 (1.65)	29.92 (2.01)	0.005 ^a
Median (Min–Max)	31.45 (28.1–34.1)	30.6 (26.5–33.2)	
Length of menopause [<i>n</i> (%)]			
Mean (SD)	9.45 (7.01)	–	
Median (Min–Max)	7 (3–31)	–	
<5 years	3 (13.6)	–	
5–10 years	14 (63.6)	–	
>10 years	5 (22.7)	–	
Education [<i>n</i> (%)]			
Elementary school	2 (9.1)	0	0.400 ^b
Junior high school	3 (13.6)	3 (13.6)	
Senior high school	11 (50)	15 (68.2)	
College	6 (27.3)	4 (18.2)	
Smoking habit [<i>n</i> (%)]			
Yes	0	14 (63.6)	<0.001 ^c
No	22 (100)	8 (36.4)	
Family history [<i>n</i> (%)]			
Yes	4 (18.2)	18 (81.8)	<0.001 ^d
No	18 (81.8)	4 (18.2)	
History of DM [<i>n</i> (%)]			
Yes	7 (31.8)	4 (18.2)	0.296 ^d
No	15 (68.2)	18 (81.8)	
History of hypertension [<i>n</i> (%)]			
Yes	17 (77.3)	15 (68.2)	0.498 ^d
No	5 (22.7)	7 (31.8)	

^aThe difference between groups is significant based on an independent *t*-test, while other letters might correspond to different tests or comparisons

Table 2: Differences in levels of IL-6, total cholesterol, HDL, LDL, and triglycerides

Variable	Woman menopause age	Woman reproductive age	p
IL-6 (pg/dL)			
Mean (SD)	58.86 (7.30)	42.23 (4.41)	<0.001 ^a
Median (Min–Max)	56 (52–81)	41.5 (36–48)	
Total cholesterol (mg/dL)			
Mean (SD)	241.41 (24.67)	205.64 (13.81)	<0.001 ^a
Median (Min–Max)	244 (204–278)	209 (177–225)	
HDL (mg/dL)			
Mean (SD)	46.55 (4.04)	48.68 (5.69)	0.158 ^a
Median (Min–Max)	46 (40–55)	48.5 (41–59)	
LDL (mg/dL)			
Mean (SD)	187.95 (21.85)	151.41 (15.56)	<0.001 ^a
Median (Min–Max)	186 (152–227)	154.5 (118–172)	
Triglycerides (mg/dL)			
Mean (SD)	228.45 (26.25)	195.32 (12.57)	<0.001 ^a
Median (Min–Max)	233 (184–269)	198 (169–214)	

^aIndependent t-test

Inclusion and Exclusion Criteria

The study's inclusion criteria included menopausal women with CAD and reproductive women with the disease between the ages of 15 and 49 who were willing to participate as research subjects. The exclusion criteria for this study were women who had a history of acute or chronic inflammatory disease, had received hormonal replacement therapy, had a history of using chemotherapy drugs or had a history of radiotherapy.

Data Analysis

The research commenced with the recruitment of research subjects based on inclusion and exclusion criteria, following approval from the ethical commission. Before conducting research, research subjects are given an explanation of the aims, advantages, disadvantages, and research procedures and then sign an agreement willing to take part in the research. After the research subject data are obtained, an anamnesis and examination will be carried out on the subject's basic data consisting of age, education, duration of menopause, and BMI. Women in the menopausal age-group and women in the reproductive age-group will have blood collected from the median cubital vein, placed in a vacuum tube, and transported to the laboratory. On the initial visit, blood samples were drawn and sent to the Prodia Medan Laboratory to be examined for lipid profiles and IL-6 levels. Once all the data have been collected, it is processed and statistically analyzed.

Data were analyzed descriptively to analyze frequency distribution of research subjects based on sample characteristics. Bivariate analysis was carried out using a correlation test to assess the relationship between IL-6 levels and lipid profiles in the group of women of menopausal age and women of reproductive age who experienced CAD. The results of the analysis are significant if $p < 0.05$, with a confidence level of 95%.

RESULTS

The study was attended by 44 women who were divided into two groups, namely women of menopausal age and women of reproductive age with the number of each group being 22 people

with CAD at H. Adam Malik Hospital. All research subjects met the inclusion criteria.

Characteristics of Research Subjects

The menopausal age-group's mean subject age was 58.86 years (52–81 years old). In contrast, the average age in the reproductive age-group was 42.23 years (36–48 years). Subjects in the menopausal age-group had a mean BMI of 31.55 kg/m² (28.1–34.1 kg/m²). Meanwhile, in the reproductive age-group, the average BMI was 29.92 kg/m² (26.5–33.2 kg/m²). Based on the length of menopause, the average length of menopause in subjects in the menopausal age-group was 9.45 years (3–31 years).

The highest level of education in the two groups was high school, with 11 people (50%) in the menopausal age-group and 15 people (69.2%) in the reproductive age-group. There were no subjects in the menopausal age-group who had a smoking habit, while in the reproductive age-group there were 14 people (63.6%) who had a smoking habit (Table 2).

Based on a family history of heart disease, there were 4 people (18.2%) in the menopausal age-group and 18 people (81.8%) in the reproductive age-group.

Based on the history of diabetes mellitus (DM) and hypertension, respectively in the group of menopausal women there were 7 people (31.8%) and 17 people (77.3%) while in the group of non-menopausal women there were 4 people (18.2%) and 15 people (68.2%).

Levels of IL-6, TC, HDL, LDL, and TG

The mean level of Interleukin-6 in the menopausal age-group was 58.86 pg/dL (SD = 7.30 pg/dL) while in the reproductive age-group, the mean was lower, 42.23 pg/dL (SD = 4.41 pg/dL).

The mean TC level in the menopausal age-group was 241.41 mg/dL (SD = 24.67 mg/dL) while in the reproductive age-group, the mean was lower, 205.64 mg/dL (SD = 13.81 mg/dL). There was a substantial difference in TC levels between the menopausal and reproductive age-groups, according to an independent t-test ($p < 0.001$).

Table 3: Relationship between IL-6 and lipid profile in women of menopausal age and women of reproductive age

Group	Variable	Interleukin-6	
		p*	R
Menopausal women	Total cholesterol	0.008	0.547
	HDL	0.556	-0.133
	LDL	0.005	0.580
Women of reproductive age	Triglycerides	0.006	0.565
	Total cholesterol	<0.001	0.747
	HDL	0.129	-0.334
	LDL	<0.001	0.800
	Triglycerides	<0.001	0.795

*Pearson correlation test

The reproductive age-group had a mean HDL level of 48.68 mg/dL (SD = 5.69 mg/dL), whereas the menopausal age-group had a mean of 46.55 mg/dL (SD = 4.04 mg/dL). The menopausal age-group and the reproductive age-group had significantly different HDL levels, according to an independent *t*-test ($p = 0.158$). The menopausal age-group had a mean LDL level of 187.95 mg/dL (SD = 21.85 mg/dL), whereas the reproductive age-group had a mean LDL level of 151.41 mg/dL (SD = 15.56 mg/dL). There was a substantial difference in LDL levels between the menopausal and reproductive age-groups, according to an independent *t*-test ($p < 0.001$).

In the reproductive age-group, the mean triglyceride level was 195.32 mg/dL (SD = 12.57 mg/dL); in the menopausal age-group, it was 228.45 mg/dL (SD = 26.25 mg/dL). The reproductive age-group and the menopausal age-group had significantly different LDL levels ($p < 0.001$), according to the independent *t*-test results (Table 3).

Relationship between IL-6 and Lipid Profile in Women of Menopausal Age and Women of Postmenopausal Age

Using the Pearson correlation test, a significant correlation was obtained between IL-6 levels and TC ($p = 0.008$). The resulting correlation value (r) is 0.547, which means that IL-6 levels have a positive correlation with TC levels, meaning that every increase in IL-6 levels will be followed by an increase in TC levels with a moderate level of strength ($r > 0.4-0.6$) in the menopausal age-group.

Using the Pearson correlation test, no significant relationship/correlation was found between IL6 levels and HDL ($p = 0.556$) in the menopausal age-group. A significant relationship/correlation was found using the Pearson correlation test between IL-6 levels with LDL ($p = 0.005$) and TG ($p = 0.006$) in the menopausal age-group. The correlation value (r) between IL-6 and LDL levels and TG in menopausal women is 0.580 and 0.565, which means that an increase in IL-6 will be followed by an increase in LDL and triglyceride levels with moderate correlation strength.

Relationship between IL-6 and Lipid Profile in Women of Menopausal Age and Women of Reproductive Age

Using the Pearson correlation test, no significant relationship/correlation was found between IL-6 levels and HDL ($p = 0.129$) in

the reproductive age-group. But IL-6 was shown to be significantly correlated with LDL ($p < 0.001$), TC ($p < 0.001$), and triglycerides ($p < 0.001$). Strong correlations are shown by the correlation values (r) of 0.747, 0.800, and 0.795 between IL-6 and TC, LDL, and triglycerides.

A significant relationship ($p = 0.006$) was observed between the duration of menopause and IL-6 levels using the Spearman correlation test. The resulting correlation value (r) is 0.567, which means that the length of menopause has a positive correlation with IL-6 levels, meaning that every increase in the duration of menopause will be followed by an increase in IL-6 levels with a moderate level of strength ($r > 0.4-0.6$) in the menopausal age-group. The duration of menopause did not appear to be significantly correlated with TC, HDL, LDL, or triglyceride levels ($p > 0.05$) (Figs 1 and 2).

DISCUSSION

Frequency Distribution

The average age and BMI were found to be higher in the menopausal age-group compared with the reproductive age-group in the characteristic data. This is consistent with research from Egypt done in 2020 that examined the connection between lipid profile, cardiac problems, and IL-6. The study found that aging will affect lipid metabolism. Increasing age and BMI will have an impact on increasing the risk of heart disease, especially in old age.¹⁰

In addition to aging, numerous research on postmenopausal women also reveal elevations in proinflammatory blood markers, particularly IL-6, following menopause, indicating that immune system alterations are linked to estrogen shortage. Several studies have linked high serum IL-6 levels (>1 pg/mL) to subclinical CAD and have shown that these levels are predictive of coronary stenosis $\geq 30\%$ in individuals at intermediate risk referred for coronary angiography.¹¹

Based on the history of DM and hypertension, respectively, in the group of menopausal women there were 7 people (31.8%) and 17 people (77.3%) while in the group of non-menopausal women there were 4 people (18.2%) and 15 people (68.2%). Several clinical research found a correlation between diabetes and insulin resistance and cardiovascular risk. Increases in TG, TC, LDL-C, and Lp(a) are linked to menopause. The HDL-C levels steadily decrease after menopause, despite the fact that women's concentrations of the lipoprotein cholesterol are constantly significantly higher than men's; this finding is considered to be advantageous for female patients.^{12,13}

Differences in Levels of IL-6, TC, HDL, LDL, and TG

The primary function of IL-6 is to regulate the acute phase inflammatory response. But it is also well recognized that IL-6 plays a significant part in the transition from acute to chronic inflammation. According to this study, lipid profiles and IL-6 levels varied significantly throughout age-groups.¹¹

Despite the influence of numerous potential confounders, such as major metabolic syndrome (TG, fasting insulin, diabetes, hypertension, BMI, waist circumference), and lifestyle habits (smoking, alcohol consumption, and physical activity), low HDL-C is linked to high plasma IL-6 levels. These conditions are frequently linked to significant changes in plasma levels of both HDL-C and IL-6. In individuals over 65, IL-6 is a factor that independently contributes to low HDL-C levels.¹¹

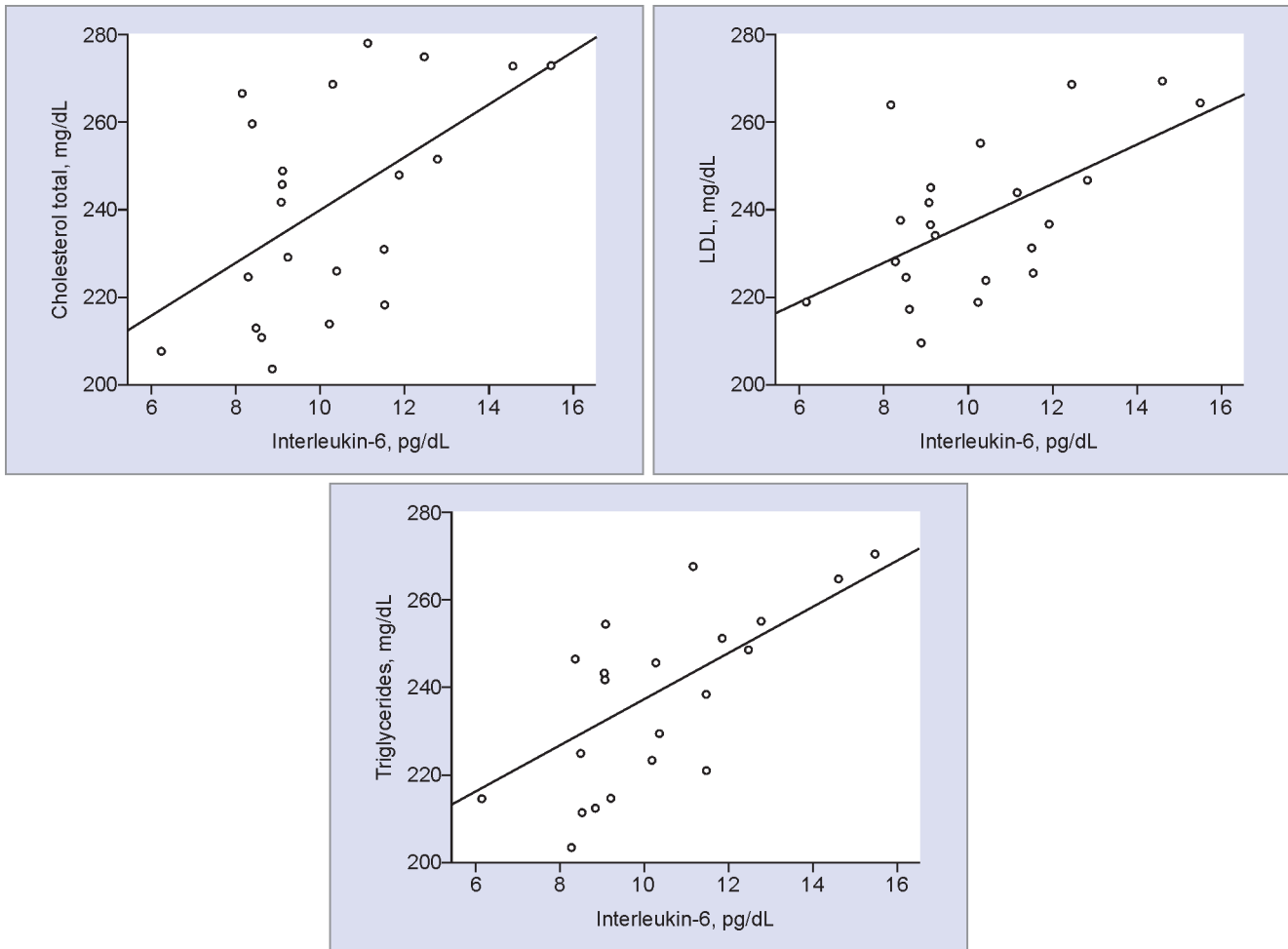


Fig. 1: Correlation of interleukin-6 with TC, LDL, and triglycerides in the menopausal age-group

Low amounts of HDL-C could be the result of changes brought on by cytokines in the particles, such as IL-6. Reduced HDL-C levels may either directly or indirectly cause elevated IL-6 plasma levels through their link to atherosclerosis. It has been shown that the main apoprotein of HDL particles, Apo AI, has strong anti-inflammatory properties. This is because it prevents activated T cells from directly activating monocytes through contact, which reduces the release of IL-1 β and TNF- α . The inflammatory cascade will be easier to activate when there is a disruption in the inhibitory mechanism caused by low HDL-C and apo AI levels.¹¹

Relationship between IL-6 and Lipid Profile in Women of Menopausal Age and Women of Reproductive Age

Hypercholesterolemia, increased lipid levels after menopause, and the role of IL-6 in lipid metabolism may influence cardiovascular risk in women. Interleukin-6 can increase free fatty acids and TG, and contribute to atherogenesis through changes in atherosclerotic plaque and influence on endothelial permeability. Post-menopausal

women tend to experience increases in TC, LDL-c, and triglycerides, while HDL-c decreases.^{14,15}

Association of Duration of Menopause with IL-6 and Lipid Profile

Studies by Lou et al. show that postmenopausal women with longer menopausal durations have greater atherogenic lipid profiles. Lowered blood HDL-C levels have been shown to be an independent risk factor for CHD in a number of investigations. This highlights the significance of screening for dyslipidemia, managing cardiovascular risk in older women, and learning more about the connection between menopause and lipid levels in order to prevent and treat CAD.¹⁶

CONCLUSION

The lipid profile (TC, LDP, and TG) and IL-6 levels are significantly correlated in women with CAD who are menopausal and of reproductive age.

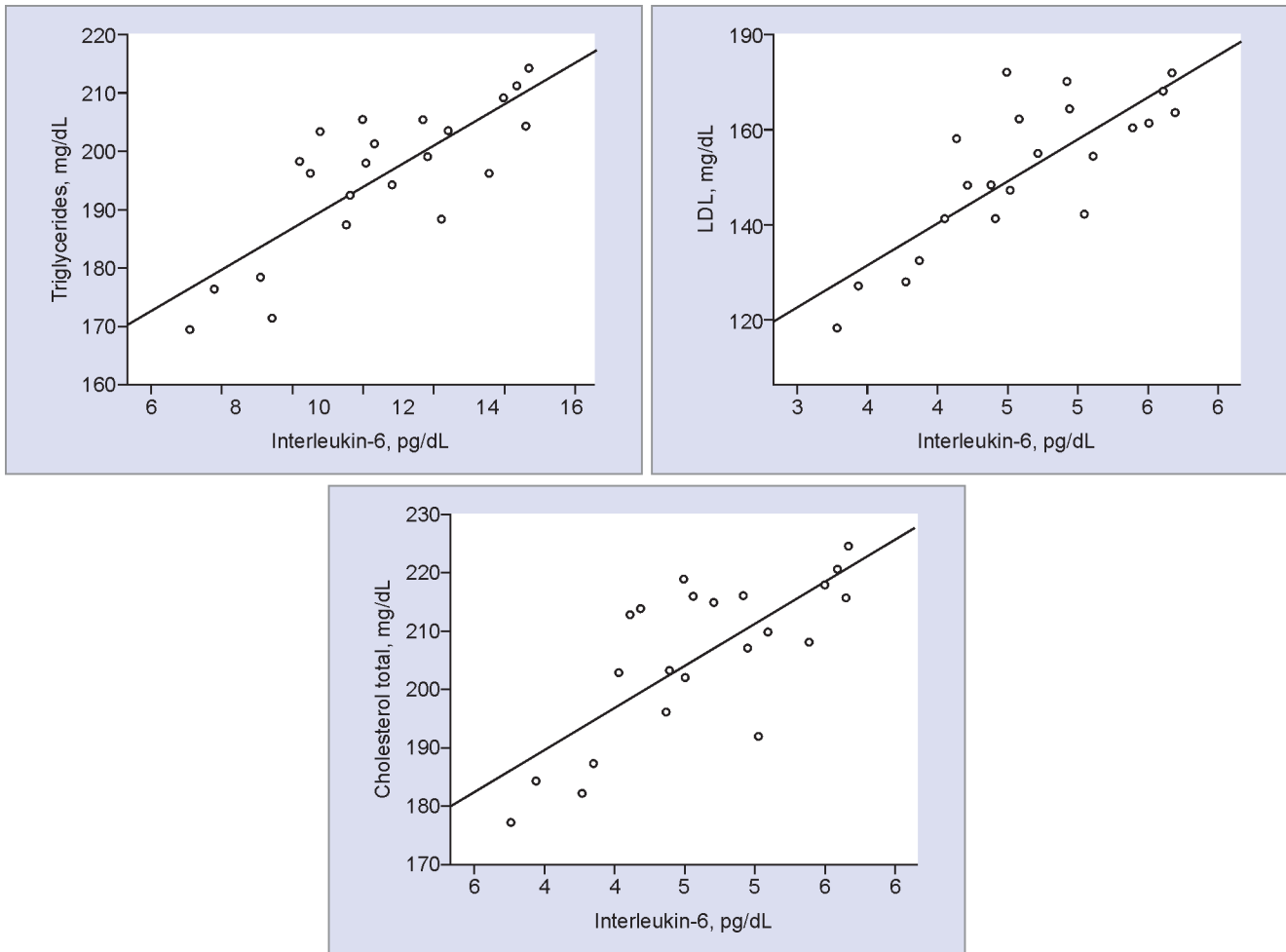


Fig. 2: Correlation of interleukin-6 with TC, LDL, and triglycerides in the reproductive age-group

Clinical Significance

Increased IL-6 is linked to lipid profile disruption in CAD patients who are menopausal or in reproductive age.

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