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Elevation of serum interleukine-6 in hypoalphalipoproteinemia patients A proinflammatory condition

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Abstract---HDL molecules have an established role in the regression processes of atherosclerosis as well as a putative role as anti-inflammatory agents. Our study investigated whether hypoalphalipoproteinemia, characterized by very low HDL levels, might be associated with increased inflammation markers such as Interleukine-6. In this study, (60) patients with HA were taken, were compared with 40 healthy controls, where the patients group were divided into two groups, the first group: HA without CHD group: included thirty (30) patients with hypoalphalipoproteinemia and without coronary heart disease aged (31-60 years). The second group: HA with CHD: included thirty (30) patients with hypoalphalipoproteinemia and coronary heart disease, documented by angiography aged (31-60 years). Control group: included forty (40) supposed healthy subjects aged (31-60 years). The results showed a significant increase in the levels of (IL-6) in all groups of patients compared to control groups ($P < 0.05$). In the patient group, IL-6 values were significantly higher in subjects with angiographically documented coronary atherosclerotic disease than in those without. Moreover, IL-6 concentrations were inversely correlated with HDL cholesterol. Also our study shows that negative correlation between HDL and (Total cholesterol, TG, LDL, VLDL, Atherogenic index and HS-CRP). Our study shows that elevation of IL-6 values in HA, in the absence of signs and symptoms of local or systemic inflammation or systemic or recurrent disease, may suggest an up regulation of proinflammatory mechanisms, which is further exacerbated by the presence of coronary atherosclerotic disease.

Keywords---HA, Hypoalphalipoproteinemia, IL-6, Interleukin-6, Inflammation.

Introduction

Large epidemiological studies have shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) are associated with increased incidence of coronary heart disease (CHD). It has been also reported that low HDL levels represent one of the most prevalent lipid abnormality in the subjects affected by CHD, and unlike high total cholesterol (TC) levels, low HDL-C levels seem to maintain a significant predictive value for CHD in the older population. Therefore, several recent guidelines⁽¹⁾ consider low HDL-C levels a strong and independent risk factor for CHD. The fact that low HDL-C is a powerful predictor of CHD has generated a considerable and growing interest about possible interventions aimed to increase circulating HDL-C levels. Very recently it has been reported that increasing HDL-C by pharmacological and life style interventions helps to prevent the angiographic progression of coronary stenosis and cardiovascular events⁽²⁾. Hypoalphalipo-proteinemia (HA) is a dyslipidemia in which HDL-C levels are less than 1.04 mmol/L (40 mg/dL)⁽¹⁾. HDL (High Density Lipoprotein) is a multi-functional lipoprotein particle that plays an important role in lipid metabolism and disease prevention^(3,4), by transporting excess cholesterol from tissues to the liver for elimination, protecting endothelial cell function, inhibiting LDL oxidation and platelet aggregation, engaging in lipid metabolism by passing the lipase cofactor and receptor. The underlying pathology of coronary heart disease (CHD) is atherosclerosis, which is an inflammatory disease. Inflammation plays a crucial role in the destabilization and rupture of atherosclerotic plaques, leading to acute cardiovascular (CV) events, at both the focal and systemic levels. Inflammation plays a crucial role in the initiation and progression of atherosclerosis⁽⁵⁾. As a mediator propagating the inflammatory response, interleukin-6 (IL6) is an essential upstream inflammatory cytokine for the initiation and progression of the atherosclerotic phase⁽⁶⁾. There is a clear correlation between IL-6 and the development of atherosclerosis that is independent of significant cardiovascular risk factors and other inflammatory and haemostatic markers. IL-6 is a pro-inflammatory and pro-coagulant cytokine that may play a role in the development and progression of atherosclerosis. In reality, IL-6 stimulates the development of a number of inflammatory and hemostatic molecules, which have been linked to atherosclerosis and thrombotic complications. For starters, IL-6 stimulates the liver's development of CRP, fibrinogen, and other acute phase reactants. IL-6 also raises basal glucose consumption, alters insulin sensitivity, and allows endothelial cells to express adhesion molecules and secrete other cytokines. Upstream IL-6 stimulates the synthesis of the downstream acute-phase reactant C-reactive protein in the liver (CRP). Several inflammatory biomarkers, such as IL-6, have been related to and used to predict the risk of cardiovascular events⁽⁷⁾, adding to the evidence for the inflammation theory. These markers have been related to a number of events in both healthy and ill people⁽⁸⁾, as well as patients with acute coronary syndrome⁽⁹⁾. In patients with stable coronary heart disease (CHD), clinical characteristics and biomarkers indicating dysglycemia, dyslipidemia, renal dysfunction, and possibly inflammatory biomarkers, such as white blood cell (WBC) counts, are used to determine the risk of events⁽¹⁰⁾. Previous research has linked WBC count to cardiovascular mortality. In this group, it's unclear how much IL-6 and HS-CRP are related to cardiovascular and non-cardiovascular events⁽¹¹⁾.

Materials and Methods

Design of Study

This study was conducted at AL- Nasiriyah Heart Center, and specialist clinicals at the period between (October 2020) to (April 2021). It included (100) subjects, control (40) and patients (60) as shown in table (1).

Table (1): Data of patients and controls groups

Study groups	No.
Patients	60
Controls	40
Total	100

The controls and patients were divided into the groups:

- **Control group:** included forty (40) supposed healthy subjects aged (31 -60 years).
- **HA without CHD group:** included thirty (30) patients with hypoalphalipoproteinemia and without coronary heart disease aged (31-60 years).
- **HA with CHD:** included thirty (30) patients with hypoalphalipoproteinemia and coronary heart disease , documented by angiography aged (31-60 years).

Collection of Blood Samples

About (5mL) of venous blood samples of cardiac catheterization patients and controls were taken and allowed to clot at room temperature in empty gel tubes centrifuge to separate it in the centrifuge at 3000 rotor per minute (rpm) for 10min. The serum samples were separated and stored at (-20°C) for later measurement of biochemical parameters, unless used immediately.

Statistical Analysis

The statistical analysis proceeded in all groups of the present study, descriptive statistics analyzed by using one-way analysis of variance (ANOVA) were performed using mean and standard deviations (SDs) with least significant difference (LSD) test for continuous variables (p value ≤ 0.05) was considered to be significant. All analyses were performed with the Statistical Package for the Social Sciences software SPSS for Windows (version 23.0, SPSS Inc., Chicago, III). As for the correlations, they were expressed by Pearson correlation coefficient (r).

Results and Discussion

Several lines of evidence indicate that inflammation may play an important part in the initiation and progression of atherosclerosis ⁽¹²⁾. HDL molecules have an intriguing role in the development of atherosclerosis because they can either protect from or accelerate that process. The latter function may be explained by the fact that HDL can act as a proinflammatory agent, as has been shown experimentally ⁽¹³⁾. Reduced concentrations of HDL may be found in a number of clinical conditions characterized or complicated by inflammatory phenomena;

indeed, HDL molecules themselves are considered to be components of acute phase response ⁽¹⁴⁾.

Interleukin 6 (IL-6)

Figure (1) show a significant increase in the concentration of serum IL-6 in patients groups in comparison with controls group ($p < 0.05$). It was found a significant increase in the concentration of IL-6 serum in HA with CHD group in comparison with (HA without CHD group $p < 0.05$). These results agree with the other studies, which have shown that IL-6 concentrations was found to be significantly increased in subjects with incident CHD compared with healthy individuals⁽¹⁵⁾. Inflammation plays a pivotal role in atherosclerosis. Several inflammatory biomarkers have been extensively studied and have found to predict the development of CAD^(16,17). Remarkably, hs-CRP is the most important related inflammatory biomarker with an increased risk of CHD development. However, IL-6, seems to be a more likely causal factor of CHD if compared to hs-CRP^(18,19). In one study, the area under the ROC curve of IL-6 was larger than hs-CRP to predict CHD, indicating that it may be more accurate. This may be explained due to the fact that IL-6 plays an earlier and more central role in pro-inflammatory regulation process⁽²⁰⁾. IL-6, together with other cytokines, might influence HDL-C levels by modifying the activity of the triglycerides lipases. It has been shown that pro-inflammatory cytokines inhibit the activity of lipoprotein lipase (LPL), and enhance the lipolytic activity of endothelial lipase (EL), Both these actions have been associated with low HDL-c levels during acute or chronic inflammatory states ⁽²¹⁾.

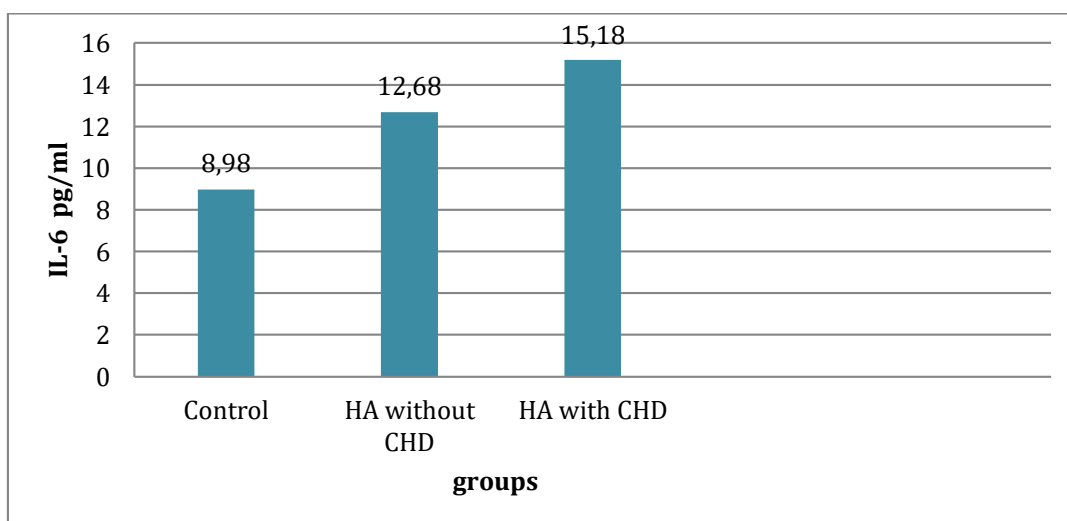


Figure (1): IL-6 values in controls and the 2 HA subgroups with and without CHD

Serum Total Cholesterol Concentration (TC)

Figure (2) shows the negative correlation between serum HDL and TC in (HA without CHD) with correlation coefficient ($r = -0.039$, $P = 0.836$) and (HA with CHD) with correlation coefficient ($r = -0.572$, $P = 0.001$).

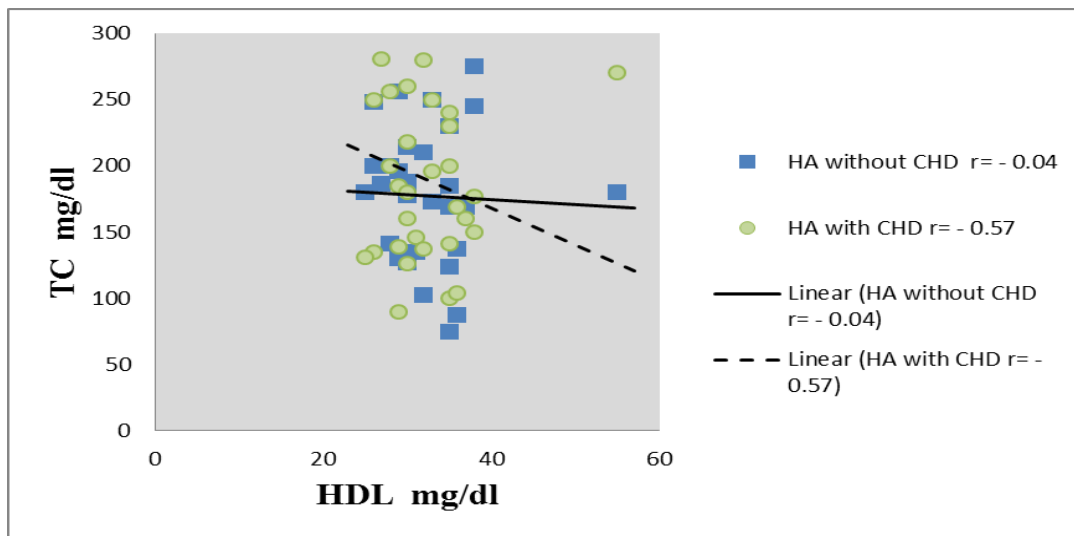


Fig (2): Correlation Between HDL and TC in Groups patients

Serum Triglyceride Concentration

Figure (3) shows the negative correlation between serum HDL and TG in (HA without CHD) with correlation coefficient ($r = -0.124$, $P = 0.512$) and (HA with CHD) with correlation coefficient ($r = -0.587$, $P = 0.001$). And this result is consistent with a previous study, where high triglycerides concentrations were found in HA group compared than control group⁽²²⁾. A reduction of HDL-C is recognized as an important risk factor for coronary heart disease. It is well known that some low HDL-C subjects have elevated TG levels⁽²³⁾.

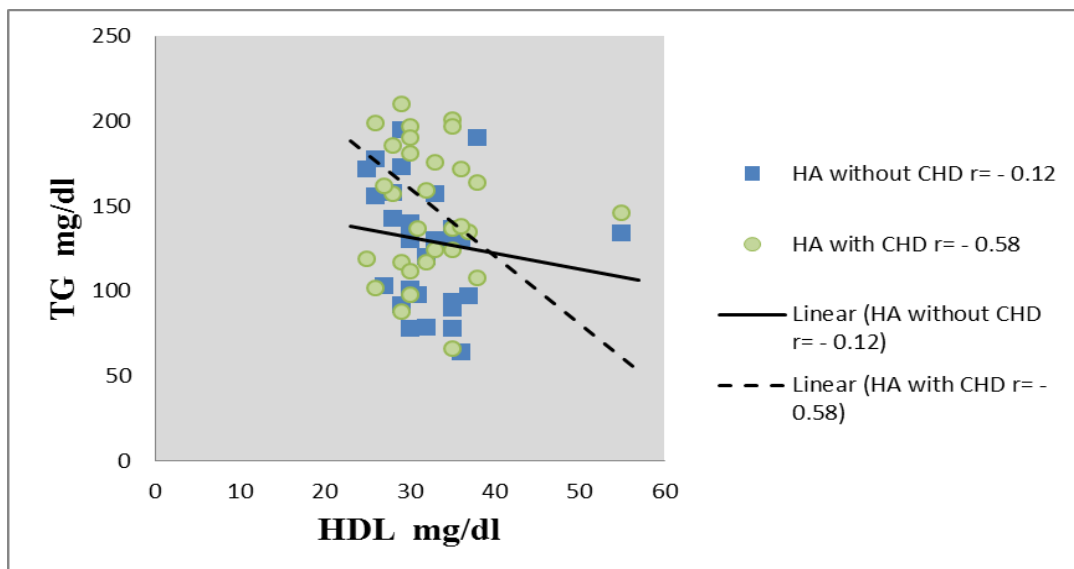


Fig (3): Correlation Between HDL and TG in Groups patients

Serum Low density Lipoprotein (LDL)

figure (4) shows the negative correlation between serum HDL and LDL cholesterol in (HA without CHD) with correlation coefficient ($r = -0.071$, $P = 0.710$) and (HA with CHD) with correlation coefficient ($r = -0.526$, $P = 0.003$).

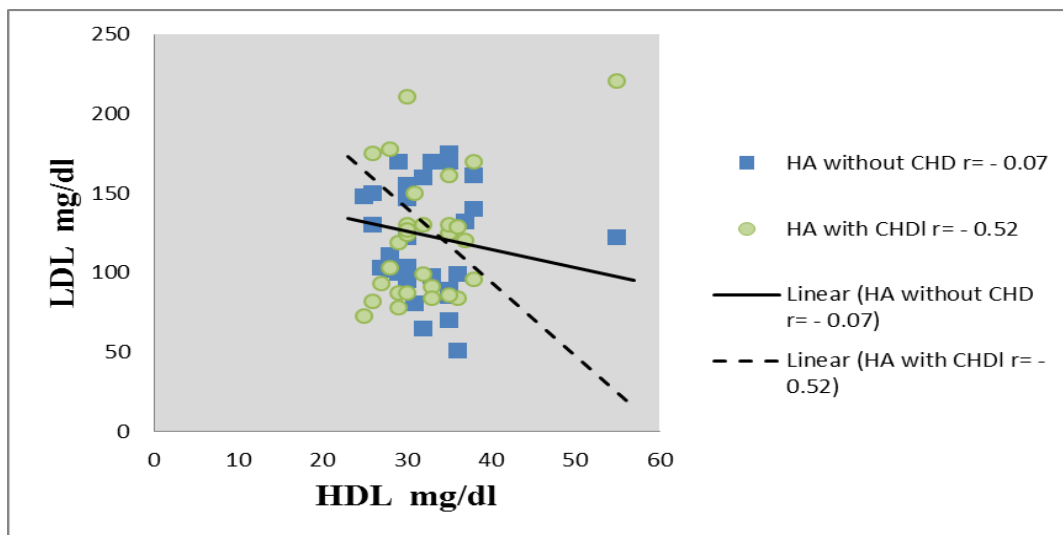


Fig (4): Correlation Between HDL and LDL in Groups patients

Serum Very Low Density Lipoprotein (VLDL)

Figure (5) shows the negative correlation between serum HDL and VLDL in (HA without CHD) with correlation coefficient ($r = -0.359$, $P = 0.051$) and (HA with CHD) with correlation coefficient ($r = -0.731$, $P = 0.000$).

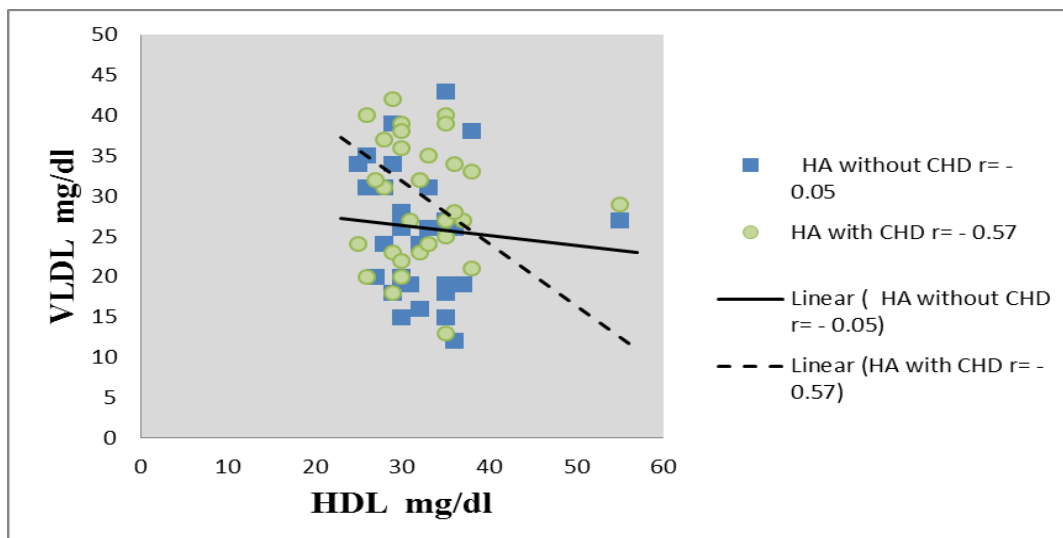


Fig (5): Correlation Between HDL and VLDL in Groups patients

Atherogenic index: Figure (6) shows the negative correlation between serum HDL and AI in (HA

without CHD) with correlation coefficient ($r = -0.359$, $P = 0.051$) and (HA with CHD) with correlation coefficient ($r = -0.731$, $P = 0.000$).

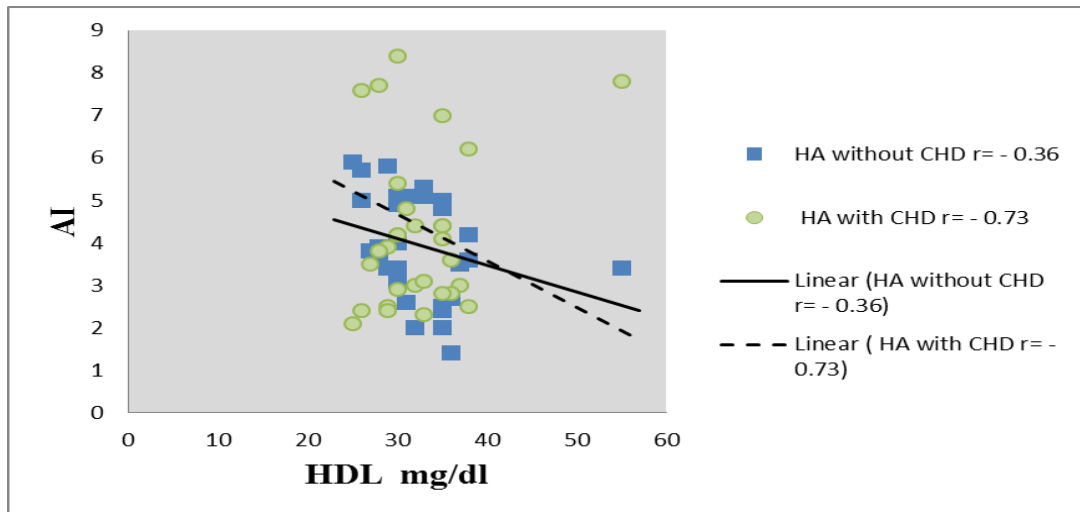


Fig (6): Correlation Between HDL and AI in Groups patients

High Sensitivity C-Reactive Protein (hs-CRP)

Figure (7) shows the negative correlation between serum HDL and HS-CRP in (HA without CHD) with correlation coefficient ($r = -0.075$, $P = 0.051$) and (HA with CHD) with correlation coefficient ($r = -0.223$, $P = 0.236$). This result matched with the results of study of ⁽²⁴⁾.

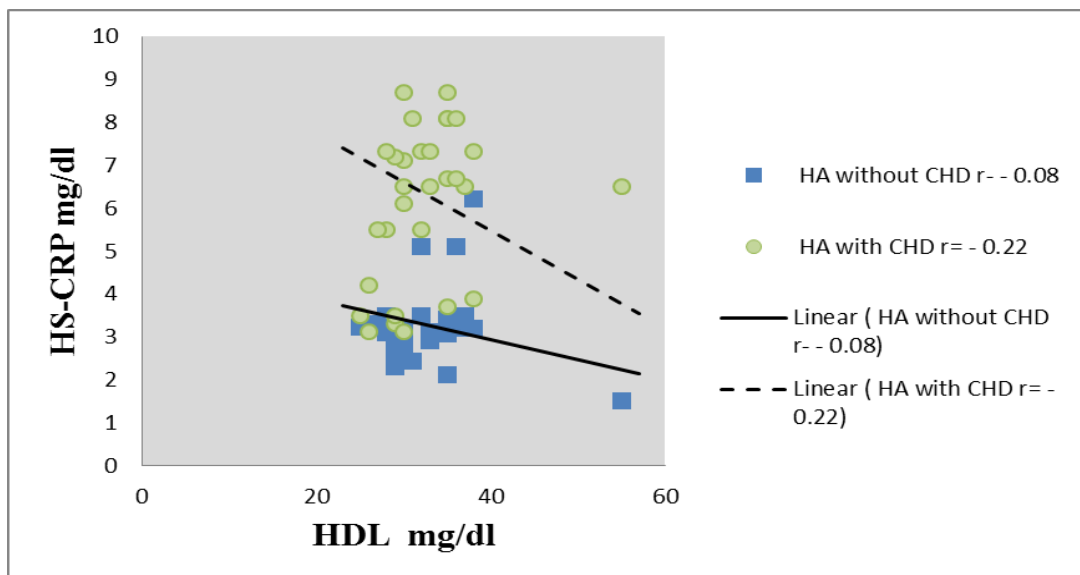


Fig (7): Correlation Between HDL and HS-CRP in Groups patients

Figure (8) shows the negative correlation between serum HDL and IL-6 in (HA without CHD) with correlation coefficient ($r = -0.031$, $P = 0.869$) and (HA with CHD) with correlation coefficient ($r = -0.262$, $P = 0.163$).

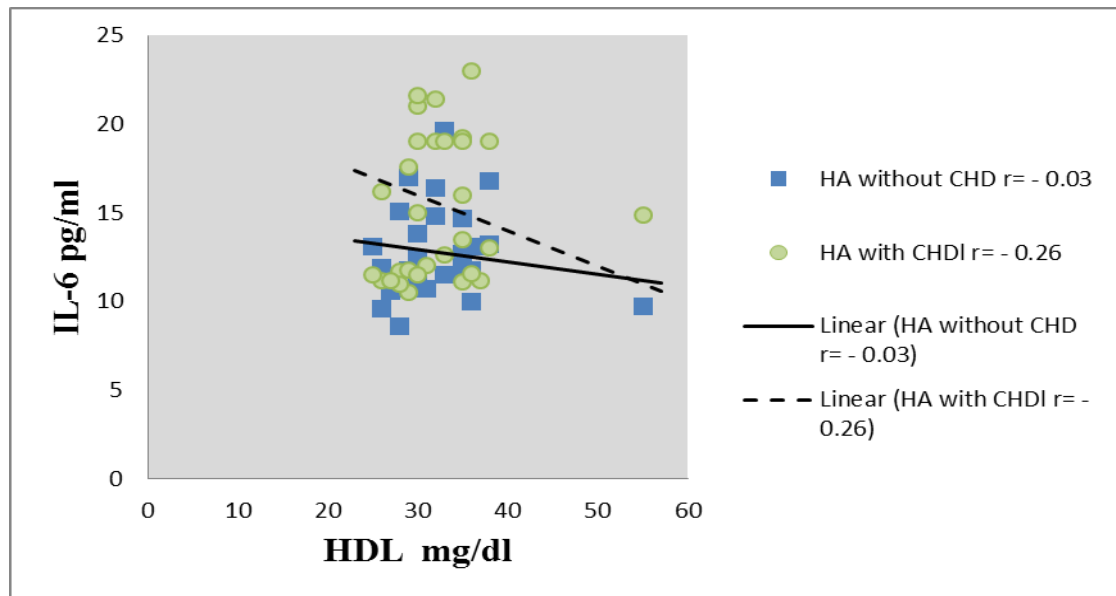


Fig (8): Correlation Between HDL and IL-6 in Groups patients

Conclusion

Although the limited number of subjects in this study suggests that we should proceed with the caution, the (1) higher IL-6 values in HA patients, (2) inverse correlation between HDL and IL-6 in HA patients, and (3) higher IL-6 concentration in HA patients with CHD indicate that HA may prove to be a useful clinical model for investigating the relationship between low HDL levels (the unique variable in HA), inflammation, and atherosclerosis.

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