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Hdl-Paradox and Cardiovascular Risks During Statin Therapy in Chronic Stable Angina

KEYWORDS: Statin therapy – HDL-paradox – Cardiovascular risk

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ABSTRACT *Background*

Lipid lowering agents became the cornerstone in treatment of coronary artery diseases, however in some cases, the good HDL-cholesterol is also reduced and described this phenomenon as "HDL-paradox". HDL-C is an independent, negative risk factor for cardiovascular disease.

Aim of the study

The aim of this study is to observe the effect of using a long term statin therapy on HDL level and its correlation to clinical course of the disease and laboratory findings in those patients.

Methods

Retrospective analysis of 210 patients known as "chronic-stable-angina" on chronic statin therapy recruited from cardiology outpatient clinic in Minia University Hospital along two years from March 2013 till April 2015. Recorded data from all patients as regard clinical and demographic data were analyzed and correlated to their symptoms and laboratory findings after dividing them onto two groups based on their averaged serum HDL-cholesterol, (group-I) with high HDL and (group-II) with Low HDL. Exclusion criteria were, known history of diabetes, hypertension, renal or liver disease, thyroid dysfunction and all participants were non-smokers. Also, obese patients with body mass index more than 30 were excluded and no cases are treated by diuretics.

Results

In spite reduction of all Non-HDL lipoproteins in both groups, significant reduction of HDL was evident in group-II and was associated with elevation in HBA1C, Hs-CRP, Proteinuria and creatinine levels. Also, liver enzymes were significantly higher in low HDL arm. A significantly lower EF ad FS% was observed in low HDL-group. Data concerning complaints and events occurred during the study period revealed that, patients of group-II having recurrent hospital admissions, more symptoms of Lv dysfunction, increasing need for modification of treatment and need for intervention more than group-I.

A linear negative correlation was found between HDL-levels and HBA1C and hs-CRP.

Conclusion

There's a significant reduction of HDL levels during long-term statin therapy 'HDL-paradox'. This is not just a laboratory observation, it's linked to deterioration of the clinical condition and cardiac functions in echocardiography. Also, change in glucose metabolism in the form of elevated HBA1C that might be a factor in appearance of new onset diabetes. The risk appeared again from elevation of hs-CRP which represent a risk factor for atherosclerosis and vascular injury. So, we advice to carefully monitoring the lipogram of all patients treated by statins and detect any significant reduction of HDL.

INTRODUCTION

HDL is widely known as a scavenger lipoprotein, this name is gained through its small size and ability to penetrate the vascular endothelium to the intima and absorb excess cholesterol from macrophages in the arterial wall then transport it to the liver or exchange it with apo B-containing lipoproteins, this process is termed as (Direct reverse cholesterol transport).[1]

Mature HDL have a spherical shape and consist of a hydrophobic core (cholesterol esters, triglycerides) and a cap that contains free cholesterol, phospholipids, apolipoproteins and enzymes including paraoxonase 1 (PON-1), lecithin-cholesterol acyltransferase (LCAT) and CETP.[2]

Precursors of mature HDL are lipid-free apo A-I particles which then transform into lipid-poor discoid pre-β1-HDL. By binding to the ABCA1 transporter, pre-β1-HDL acquire phospholipids and non-esterified cholesterol from the surface of various cells including macrophages. LCAT present in these lipoproteins catalyses cholesterol esterification on their surface. Cholesterol esters then migrate to the core, leaving lipoprotein surface free to accept free cholesterol.[3]

This process results in formation of larger HDL3 particles which also accept free cholesterol from cells. Cholesterol esterification by the action of LCAT takes place also in HDL3. As a result of these two processes,HDL 3 particles are transformed into even larger HDL2 particles.[4]

The SRBI scavenging receptor on hepatocytes removes cholesterol from HDL 2 and regenerates pre-β1 HDL and HDL 3 from HDL2. The main role of HDL is to remove excess cholesterol from cells (reverse cholesterol transport) and HDL maturation or transformation of small into larger HDL particles is a prerequisite for normal reverse cholesterol transport.[5]

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The well known antiatherogenic role of HDL is supported in many trials, Khera et al.[6] reported that the ability of HDL to accept cholesterol from cultured macrophages showed a negative association with coronary events regardless of HDL-C level. The authors found that the coronary event risk decreased by 30% for each increase of the ability to remove cholesterol from macrophages.

In addition, a significant negative correlation was found between the ability of HDL to accept cholesterol from macrophages ex vivo and the carotid artery intima–media thickness, even when adjusted for HDL-C level. Recently, Khera and Rader [6,7] summarized the current knowledge on complex links between cholesterol removal from macrophages by HDL and atherogenesis in an editorial article published in a prestigious journal devoted to research on atherosclerosis.

Evidence of the role of HDL in reverse cholesterol transport were also provided by the studies on the use of HDL infusion to treat atherosclerosis, summarised in a recent review paper by Kingwell and Chapman[8]. Intravenous HDL infusions remove cholesterol from atherosclerotic plaques and reduce their macrophage content which may have an effect on plaque stabilisation and/or regression.[8]

The anticoagulant effect of HDL is related to a reduced expression of tissue factor on endothelial cells and inhibition of platelet activation. In vitro studies showed that HDL reduce platelet aggregation induced by collagen, thrombin, and adenosine diposphate. These lipoproteins may also inhibit thrombus formation by maintaining the integrity of endothelial cells. In addition, HDL stimulate prostacyclin synthesis.[9]

Stimulation of nitric oxide (NO) synthesis and expression of an antiapoptotic Bel-xL protein should also be mentioned among the antiatherogenic effects of HDL. Evidence is available from in vitro studies that HDL protect LDL from oxidation. Lipid peroxides may be transferred from LDL to HDL to be metabolised in the latter. The ability of HDL to reduce accumulation of lipid peroxides is associated mostly with apo A-I and PON-1 activity.[10]

HDL also play a role in glucose homeostasis. Low HDL-C level may increase the risk of the development of type-II diabetes and always associated with insulin resistance. Genetic defects leading to low HDL-C level are associated with impaired insulin secretion and increased resistance to insulin. The low HDL cholesterol/high triglyceride pattern is associated with the degree of hyperglycemia. In coronary patients with type 2 diabetes, this pattern correlates with the prevalence of CAD and significantly predicts the incidence of vascular events. An infusion of reconstituted HDL reduced blood glucose level in patients with type-II diabetes.[11]

Patients and Methods

Retrospective analysis of 210 patients known as "chronic-stable-angina" on chronic fixed dose of statin therapy (20 mg Atorvastatin) in conjunction with other anti-ischemic regimens was done through collection of their data from cardiology outpatient clinic in Minia University Hospital along two years from March 2013 till April 2015.

All patients clinical and demographic data were recorded, patients were instructed to record their clinical data including (frequency of chest pain, average distance of anginal pain, numbers of hospital admissions, symptoms of Lv dysfunction, Need to increase nitrates or other therapy dosages, and need for invasive strategies) and bring it to his physician in the regular 15-days follow up. Data are then averaged for each patient respectively .

Regular ECG using Fukuda Denshi Climax machine (filter range 0.5 Hz to 150 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV) was done for all patients. Echocardiography Data were also recorded using a commercially available GE vivid 3 echo machine equipped with 2.5–3.5 MHz transducer was done for all patients to measure Lv dimensions and functions including (LVEED, LVESD, FS and EF %). All data were averaged at the end of two years.

Three month laboratory analysis of (Lipid profile, HGA1C, High sensitivity-CRP, Proteinuria, serum creatinine and liver enzymes) were also recorded and averaged for each participant.

Exclusion criteria were (known history of diabetes, hypertension, renal or liver disease, thyroid dysfunction and all participants were non-smokers) Also, obese patients with body mass index more than 30 were excluded and no cases are treated by diuretics.

Patients were then divided –according to their HDL level– into two groups :-

(Group-I) with High HDL more than 60 mg/dl = they were 163 patient and,

(Group-II) patients with low HDL values less than 40 mg/dl = they were 47 patient

Statistical analysis:

Data was presented as numbers and frequencies for categorical variables, and mean ± standard deviation or median values for continuous variables. The continuous variables were analyzed for normality. P value less than 0.05 was considered statistically significant. The Pearson correlation coefficient was computed to examine the association between two continuous variables.

Results

Comparison of demographic data between both groups is shown in Table (1) and revealed a non-significant variations between both groups

Table (1): patients demographic data

	Group-I (High HDL) N= 163 (77.6%)	Group-II (Low HDL) N= 47 (22.4%)	P
Age (yrs)	51 ± 7	50 ± 8	NS
Height (cm)	172 ± 4	176 ± 2	NS
Weight (kg)	85 ± 4	84 ± 4	NS
BMI (kg/m2)	27.3 ± 1.2	26.8 ± 2.2	NS
Gender male, n (%)	133 (82%)	39 (83%)	NS

At the end of the study, patients were divided –according to their averaged HGD level- into two groups, 163 patients with HDL> 60 mg/dl (group-I) representing 77.6% of the total cases and, 47 patients with low HDL< 40 mg/dl (group-II) representing the remaining 22.4%

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Data in each group were averaged and a statistical comparison of the findings revealed the following results:

Medications used along the whole study period

Medications used along the study period revealed non-significant variation between both groups, table (2)

Table (2): medications used during the study

Medications	Group-I	Group-II	P
ASA, n (%)	163 (100%)	47 (100%)	NS
B-Blockers, n (%)	143 (88%)	40 (86%)	NS
CCB, n (%)	20 (16%)	7 (14%)	NS
ACEI, n (%)	19 (12%)	5 (11%)	NS

Laboratory findings between pre-study and End of study period

Laboratory findings were compared in between cases pre-study (base-line data) and averaged results (after the study period) and revealed no statistical differences in all laboratory findings before the study,

Then all data were statistically different at the end of the study. In spite reduction of all Non-HDL lipoprotein in both groups, significant reduction of HDL was evident in group-II and was associated with elevation in HBA1C, Hs-CRP, Proteinuria and creatinine levels.

Also, in spite of elevation of liver enzymes after treatment in both groups, it was significantly higher in low HDL arm as shown in table (3)

Table (3): medications used during the study

Parameter	Base-line Data			End of the study		
	Group-I (↑HDL)	Group-II (↓HDL)	P	Group-I (↑HDL)	Group-II (↓HDL)	P
Lipid profile						
- total cholesterol (mg/dl)	260 ± 20	265 ± 15		210 ± 20	180 ± 15	
- Triglyceride (mg/dl)	190 ± 40	200 ± 30	NS	150 ± 14	130 ± 20	0.001
- LDL (mg/dl)	96 ± 24	110 ± 10		86 ± 24	70 ± 10	
- HDL (mg/dl)	40 ± 8	38 ± 10		68 ± 8	35 ± 5	
HBA1C (%)	5.6 ± 1.8	6.1 ± 1.2	NS	5.8 ± 0.4	6.2 ± 0.6	0.001
Hs-CRP (mg/dl)	0.82 ± 0.2	0.78 ± 0.3	NS	0.72 ± 0.2	0.88 ± 0.8	0.001
Proteinuria (ug/min)	6.3 ± 1.4	6.2 ± 1.6	NS	9.2 ± 0.8	14.5 ± 0.5	0.001
Creatinine (mg/dl)	0.9 ± 0.12	0.8 ± 0.22	NS	0.88 ± 0.2	1.2 ± 0.4	0.001
Liver enzymes						
- AST (unit/l)	26 ± 4.2	27 ± 3.0	NS	32.4 ± 2.6	40 ± 4.0	0.001
- ALT (unit/l)	42 ± 2.8	44 ± 1.0		44.0 ± 2.8	52.0 ± 2.0	

Echocardiographic findings between pre-study and End of study period

Base-line Echocardiographic data from the sheet of both patients prior to initiation of the study revealed no statistically significant results, But, at the end of the study a significant reduction in EF and FS % was detected in group-II, as shown in table (4).

Table (4): Echocardiographic findings between both groups

Parameter	Base-line Data			End of the study		
	Group-I (↑HDL)	Group-II (↓HDL)	P	Group-I (↑HDL)	Group-II (↓HDL)	P
LVEDD (mm)	50 ± 5	49 ± 4	NS	52 ± 4	53 ± 3	NS
LVESD (mm)	30 ± 4	30 ± 3	NS	33 ± 3	34 ± 2	NS
EF %	58 ± 3	57 ± 2	NS	60 ± 2	56 ± 2	0.003
FS %	25 ± 2	24 ± 2	NS	27 ± 2	24 ± 2	0.017
Tei-Index	0.54 ± 0.18	0.62 ± 0.08	NS	0.52 ± 0.1	0.6 ± 0.1	NS

Comparison of Clinical events during the study period between groups

Data of the records recruited from all patients as regarding their complaints and events occurred during the study period revealed that, patients of group-II having recurrent hospital admissions, more symptoms of Lv dysfunction, increasing need for modification of treatment and need for intervention more than group-I…. as shown in figure (1) & (2)

Figure (1) Clinical data in both groups

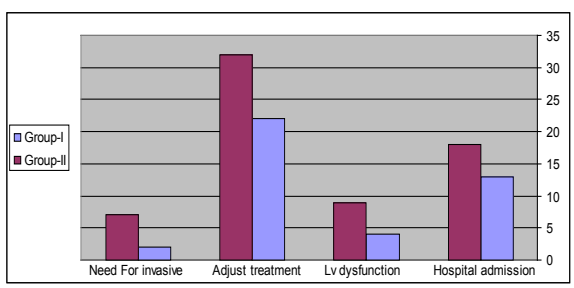
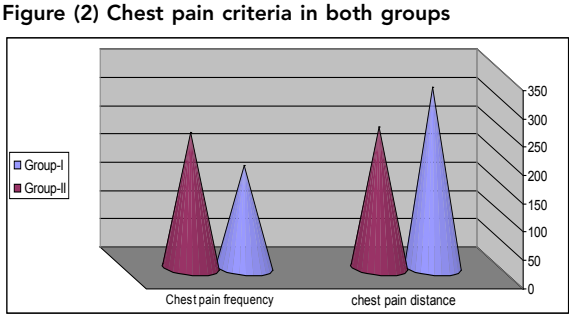


Figure (2) Chest pain criteria in both groups



Correlation between HDL level and other laboratory findings

In a trial to discover the relation between HDL and other variables, a correlation was made between HDL levels and both laboratory and Echocardiographic data:

A- Correlation between HDL and HBA_1C

A linear negative correlation was found between HDL-levels and HBA1C with Pearson correlation coefficient -.99 and p value 0.001 as shown in figure (3).

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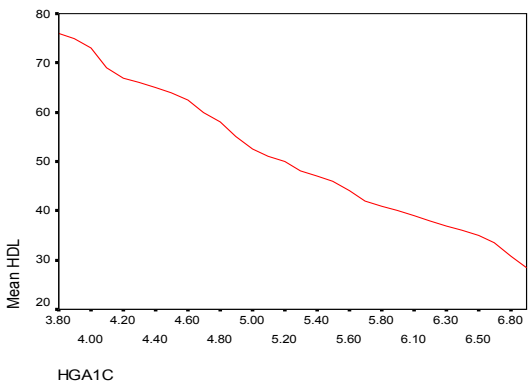
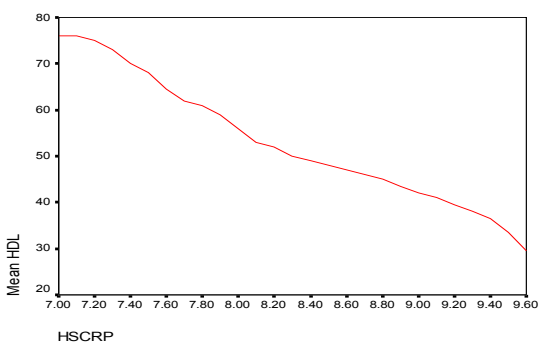
Figure (3): Correlation between HDL and HBA_1C



B- Correlation between HDL and hs-CRP

A linear negative correlation was found between HDL-levels and hs-CRP with Pearson correlation coefficient -.94 and p value 0.001 as shown in figure (4).

Figure (4): Correlation between HDL and hs-CRP



DISCUSSION

Lipid lowering agents became the cornerstone in treatment of coronary artery diseases, many authors noticed that, in some cases, the good HDL-cholesterol is also reduced after long-term statin therapy, and described this phenomenon as "HDL-paradox". HDL-C is an independent, negative risk factor for cardiovascular disease with low levels increasing the risk for disease.[12]

Many trials represented this Paradoxical decrease in HDL during treatment by Fibrates and rosiglutazone, while little is known about this phenomenon with statin therapy.[13,14]

Our study is concerned with observation of HDL level after two years of chronic statin therapy and its correlation to clinical and laboratory findings of the patients of chronic stable angina. The first observation was, deterioration of blood glucose metabolism in the form of elevation of HBA_1C and confirmed by its negative linear relation when compared to HDL level in a statistically significant result. This conclude impaired glucose metabolism and accelerate development of diabetes.

This was in agreement with a paper published by Xia et al in 2008. It was very interesting to note that lowering cholesterol by as little as 10% (molecular in cell walls) in the pancreas (pancreatic beta-cells) prevented the release of insulin (cholesterol-mediated exocytosis). [15] This paper described a mechanism by which 'cholesterol lowering drugs' directly cause diabetes.

It was known that in statin drug trials which looked at glucose (blood sugar) control there was poor blood-sugar control in the statin user groups. Since 2011 the USA government (FDA) required statins to carry a warning about the risk of causing diabetes.[16]

Our study detect a negative linear correlation between HDL level and hs-CRP. This is reflected on clinical sequences in the form of increasing frequency of chest pains, recurrent hospital admissions and need for changing treatment modalities in Low HDL-group. Also, more patients in Low-HDL arm underwent invasive treatment strategy, and this confirm progression of atherosclerosis in their coronaries.

Numerous previous data support our finding and confirm the role of elevated CRP in the process of inflammation and atherosclerosis, they also reported it as predictor for clinical risks.[17,18,19]

Authors reported that, The antiatherogenic effect of HDL is not limited to reverse cholesterol transport. We will briefly summarise these other mechanisms as recently reviewed by Soran et al.[19], Lüscher et al.[20] and Rosenson et al.[21] who published extensive reviews on this topic. HDL exert antiinflammatory, anticoagulant, and antioxidative effects. A potential antiinflammatory effect of HDL may be largely dependent on PON-1, a HDL-related antioxidant enzyme. Antioxidant HDL properties mediated by PON-1 contribute to reduction of oxidative stress and inflammation. HDL reduce production of inflammatory cytokines by macrophages and endothelial expression of adhesion molecules (ICAM-1 i VCAM-1) which facilitate penetration of monocytes and neutrophils into the arterial wall.

Some studies indicated that in patients receiving intensive lipid-lowering therapy who reached low target LDL-C levels, HDL-C level was not a risk factor or showed a weak association with the risk. In the recently reported SMART study in patients with CVD who received no lipid-lowering therapy or were on usual doses of lipid-lowering drugs, low HDL-C level was associated with an increased risk but no such association was seen in patients receiving intensive therapy.[22]

Similar results were reported in the JUPITER study in which a large rosuvastatin dose of 20 mg per day was used in healthy subjects.[23,24] . Also in the PROVE IT TIMI 22 study, HDL-C level had no predictive value in patients with an acute coronary syndrome (ACS).[17]

(ACS) receiving intensive atorvastatin therapy (80 mg/day) [17], and in the TNT study in patients with stable CAD randomised to 80 mg of atorvastatin daily the association between HDL-C level and the risk was weaker compared to the control group (atorvastatin 10 mg/day). [25]

In contrast to the above studies showing that intensive statin therapy abolished the relation between HDL-C level and the risk, the recently reported COURAGE study in patients with stable CAD who were optimally treated to a target LDL-C level of 60–85 mg/dL with lipid-lowering drugs (statin ± ezetimibe, extended-release niacin, or fibrate) showed the risk to be associated with HDL-C level. [26]

In the Heart Protection Study (HPS), patients treated with simvastatin showed an approximately 1% increase in serum HDL-C level.[27] The Collaborative Atorvastatin Diabetes Study (CARDS), patients treated with atorvastatin showed

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a 9% decrease in serum HDL-C level.[28]. In the Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) and the Treating to New Targets study (TNT), serum HDL-C barely changed. [29,30]

Although the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) demonstrated a significant improvement in serum HDL-C, this amounted to an approximately 2% elevation only.[31]

All of these large long-term statin trials show an underperformance in causing HDL-C changes in diabetic patients. Our results are in accordance with these large studies, and suggest that the improvements seen in serum HDL-C in diabetic patients under "long-term" atorvastatin and simvastatin treatment should be reassessed.

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