The Substantial effects of Statins Therapy on PCSK9 and Adipocytokine in Dyslipidemic Non-Diabetic Patients: Prevailing Motive

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Abstract

Background: A large number of cardiovascular disease (CVD) studies infavor use of statins in the management of dyslipidemia owing to their central role in reduction the morbidity and mortality among people suffering from a variety of diseases. Currently the pathophysiological studies on atherosclerosis take a more complex tract than just a lipid buildup problem. Objectives: The purpose of the present study is to evaluate the association between statins therapy and the (adipocytokine and inflammatory) mediators in dyslipidemic non-diabetic patients. Materials and Methods: A total number of 63 dyslipidemic non-diabetic patients were recruited compared with 25 healthy control people. The study were divided into; Group (A): Patients on statins therapy (n=40), Group (B): Patients were not on statins therapy (n=23), and Group(C): Healthy controls (n=25).

Results: There was substantial dyslipidemic status in patients not on statins therapy as matched to patients on statins therapy and healthy controls. TC, TG, VLDL, LDL were greater in patients not on statins therapy. Preprotein convertase subtilisin/kexin type 9 (PCSK9) serum level was higher in statins as compared to non-statins group and controls. Moreover, PCSK9 was greater in rosuvastatin than in atorvastatin treated patients. Retinol bindg protein 4 (RBP4) was lower in statins group compared to non-statins group and controls. While there was no significant difference in the level of RBP4 between atorvastatin and rosuvastatin using patients, although atorvastatin showed a lower value of RBP4. Moreover, the study showed lower level of CRP in statins group (mainly rosuvastatin) than in non-statins group.

Conclusion: Statins enhanced PCSK9 level, with a greater elevation in PCSK9 was observed in rosuvastatin treated patients in comparison to atorvastatin .Statins therapy had a protective effect in lowering RBP4 and CRP in dyslipidemic non diabetic Iraqi patients.

Keywords: adipocytokine, inflammatory mediators, statins therapy.

1. Introduction

Statins have been shown to be the most effective pharmacological treatment for lowering low-density lipoprotein (LDL) cholesterol levels, and their impacts may spread over their plasma LDL–lowering ability. Statins have an imperative role in decreasing both morbidity and mortality in dyslipidemic patients with multiple diseases and apart from cholesterol lowering influence, statins are known to have multiple properties, which are collectively known as pleiotropic effects, that include "antioxidant properties, enhance endothelial function, promote atherosclerotic plaque stability, reduction of platelets aggregation and coagulation process, in addition to the anti-inflammatory effect" Kuraishy [1].

The assumption that inflammation plays a key role in the etiology of atherosclerosis and its consequences has attracted much interest. The cellular mechanisms of inflammation that cause atherosclerosis have been exposed through many researches. The proof of identity of atherogenesis as a dynamic process rather than a cholesterol deposition disorder has brought to light several important inflammatory processes and mediators. [2]. In addition, the epidemiological and experimental evidences have considerably enhanced the pathophysiological connection between adiposity and atherosclerosis during the previous decade. In this context, Adipose tissue is now recognized as an endocrine organ that regulates a variety of physiological activities in addition to storage, via releasing several adipocytokine mediators [3].

Preprotein convertase subtilisin/kexin type 9 (PCSK9) was first recognized in 2003 in French families suffering from

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autosomal dominant hypercholesterolemia. PCSK9 is one of the nine serine proteases , which is synthesized as a zymogen , consisting of 692 amino acids.Pro-PCSK9 is synthesized in the endoplasmic reticulum .PCSK9 controls mature LDLR expression by inducing intracellular degradation of LDLR before it is transported to the cell membrane [4]. As a result, PCSK9 disturbs cholesterol level. Statins increase PCSK9 expression by increasing the transcription factor sterol –response element binding proteins (SREBP2), which controls LDLR expression. Moreover, PCSK9 stimulates the degradation of apolipoprotein E receptors-2 and raises the concentration of lipoprotein (a). In effect, this can worsen the atherosclerotic plaque by causing plaque instability, expressing of endothelial cell adhesion molecules, aggregation of monocytes and smooth muscle proliferation Through different pathways, PCSK9 has negative effects on atherosclerotic plaques, including LDL oxidation and plaque structure modifications.This gives a potential advancement in evaluating the link between different types of statins therapy and this plasma protein which has revolutionized the lipid metabolism process [5].
Retinol binding protein 4 (RBP4) is a secreted protein with approximately 21 KDa , belongs to the lipocalin family and is formed primarily by hepatocytes and visceral adipocytes.RBP4 act to transmits retinol (Vitamin A) from the liver to peripheral tissue [6].
In 2005, RBP4 has been identified as an adipokine (adipose- derived cytokine) that leads to insulin resistance. Moreover , recent trial have shown that RBP4 is an emergent proinflammatory factor that stimulates TLR4-dependent signals, causes insulin-resistant, obesity and metabolic syndrome , which had been associated with coronary plaque vulnerability.RBP4 plays a role in plaque rupture by increasing proliferation of vascular smooth muscle and stimulation of E-selectin as a plaque development indicator . A recent work found that high serum level of RBP4 is correlated with cardiovascular disease, including hypertension, atherosclerosis and CHD [7]. Furthermore, RBP4 was related independently to lipoprotein enzymes, signifying an impending role of RBP4 in lipid metabolism. In addition, higher RBP4 levels are related to higher risk of coronary artery calcification. RBP4 has been shown to be a leading characteristic of atherosclerosis by induction of inflammation , disruption of endothelial mitochondrial homeostasis resulting in endothelial dysfunction and foam cell formation , which together accelerate atherosclerosis .Some studies have shown a positive relationship between RBP4 and oxidative stress. Cellular oxidative stress causes vascular inflammation and endothelial dysfunction [8].
CRP is a pentraxin plasma protein. It was first observed in 1930.Most of the CRP is synthesized in the liver, and is mainly controlled by IL-6.CRP also formed in atherosclerotic lesions by monocytes and lymphocytic cells. Smooth muscle cells, endothelial cells and adipocytes can also produce it [9].
CRP enhances the formation of foam cells via facilitating the phagocytosis of LDL by macrophages especially “damaged” LDL. Therefore, CRP promotes the onset and progression of arteriosclerosis. Studies noted that the inhibitory effect of CRP on the production of NO may contribute to the development of cardiovascular disease. CRP can increase the size of myocardial infarction in experimental models [10].

2. Materials & Methods

This study used a case-control design , 40 patients aged between 45-70 years were enrolled from "Al-Yarmouk Teaching Hospital" , from April 2021 to Septemper 2021 , and compared with 20 healthy controls. Patients and healthy controls were divided into :
Group (A): Patients on statins therapy (n=40)
Group (B): Patients not on statins therapy (n=23)
Group (C): Healthy controls (n=25)
Inclusion criteria: patients with dyslipidemia who were above 45 years old, with or without statin medication, were included in the study.
Exclusion criteria: people with severe or morbid obesity, end-stage renal illness, liver failure, mental problems, severe anemia, connective tissue diseases, pregnancy, breastfeeding, or cancer.

Anthropometric measurements

Body mass index (BMI) was obtained from measuring the weight in kilograms & the height in meters, then BMI was calculated by specific equation : " BMI = weight (kg) / (Height (m2) " .

Biochemical measurements

Lipid profile estimation: total cholesterol (TC) , triglyceride(TG) and high density lipoprotein (HDL) were measured by auto-analyzer (ERBE diagnostic Manheim, Germany). Low density lipoprotein (LDL) was assessed by Friedewald equation [11] VLDL=TG/5 . Determination of human PCSK9 was prepared by using ELISA Kit method (MyBioSource/USA), which was stated as ng/ml. Serum RBP4 concentration was calculated by using an enzyme linked immune sorbent assay kit (MyBioSource /USA). CRP concentration was measured by enzyme linked immune sorbent assay kit (LDN / Germany).

Statistical analysis

The data was analyzed using the accessible statistical program SPSS-24 (Statistical Packages for Social Sciences, version 24). Data were provided in basic percentage, number, mean, and standard deviation measurements. Furthermore, the significance of difference of different means was assessed using an unpaired t-test for differences between two independent means and an ANOVA test for differences between more than two independent means. When the P value was less than 0.05, statistical significance was evaluated.

3. Results

Demographic characteristics of the present study

The patient and control groups appear to be closely matched in terms of age, gender, weight, height, and body mass index (BMI). The study found no significant change in body mass index (BMI) between patients with and without statin medication and controls (P=0.52)

(Table 1).

Table 1. Demographic features of dyslipidemic patients and controls

Variables		Controls (n=25)	Patients (n=63)	P
Age (years)		62.64±13.6	62.8±9.85	0.52
BMI (kg/m2)		28.30±5.52	27.66±5.39	0.44
Gender	male	18 (72 %)	46 (73%)	0.32
	female	7 (28 %)	17 (27 %)	0.52
Smoker	yes	15 (60 %)	28 (44.4%)	0.03
	No	10 (40 %)	35 (55.5 %)	0.04
PMH	Hypertension	------	31(49.2%)	
	dyslipidemia		1 (1.5%)	
	IHD		28 (44.4%)	
	CVA		7 (11.1 %)	
Life style	active	20(80%)	22(34.9%)	
	Moderate	5(20%)	17(26.9%)	
	sedentary	-------	24(38%)	

Data are expressed as n, mean ±SD, %. BMI: body mass index,PMH:past medical history ,CVA : cerebrovascular accident, IHD:ischemic heart disease.

Assessment of metabolic profile in patients with ACS

Among terms of the metabolic profile, there was a substantial dyslipidemic state in patients who were not on statin medication compared to patients who were on statin therapy and healthy controls. Patients who were not taking statins had higher levels of TC, TG, VLDL, and LDL. In terms of HDL levels, statins outperformed non-statins and controls.

Biochemical Analysis of the adipocytokine and inflammatory biomarkers in patients and controls

PCSK9 serum level was significantly differed among all studied groups (P<0.05). It was higher in statins group when compared to non-statins group. Moreover, PCSK9 was lower in controls than in patients.Concerning RBP4, there was no significant difference in all groups when compared by using ANOVA test. Although statins group had lower RBP4 when compared to non-statins. CRP level showed no significant difference among study groups when investigated by using ANOVA test, while CRP level was lower in statins group in comparison to non-statins group by (LSD test), as shown in table 3.

Table 3: adipocytokine and inflammatory biomarkers in patients and controls

Variable	Control n=25	Non –statins group n=23	Statins group n=40	P VALUE ANOVA
PCSK9 (ng/ml)	2.64±0.68	3.64±0.86 #	4.60±1.08*	**0.0001**
RBP4 (ng/ml)	42.55±28.27	#48.57±15.21	37.22±7.11	**0.051**
CRP (mg/L)	2.95±0.77	#3.04±0.90	2.57±0.85	**0.070**

Data are presented as mean ± sd , anova test and lsd post-hoc test ,pcsk9: proprotein convertase subtilisin / kexin type 9, , rbp4: retinol binding protein 4, crp: c reactive protein .
* p<0.05 compared between control with statins groups
# p<0.05 compared between statins with non-statins groups
¤ p<0.05 compared between controls with non-statins groups

4. Discussion

In terms of lipid profile, the study found lower levels of cholesterol, triglycerides, VLDL, LDL, and greater levels of HDL in statin-treated patients compared to non-statin-treated patients, which is consistent with statins' lipid-lowering impact [12] The study showed that PCSK9 serum level was higher in statins group when matched to non-statins users and controls , this is consistent with previous research , which showed that dyslipidemic patients had increased level of PCSK9, the study also revealed that patients who had prior use of statins therapy were presented with significantly higher PCSK9 levels as compared to those not on statins [1].

A number of in vivo studies have demonstrated that, hepatic PCSK9 mRNA expression was significantly increased in dyslipidemic patients who had cardiovascular ischemic events mediated by SREBP-2 and HNF1-α transcription factors. Several mechanisms have been implemented including; inflammation, injury to the muscle , and oxidation of LDL by apoptosis and necrosis of endothelial cell, all can contributes to up regulation of hepatic PCSK9.Moreover, PCSK9 has been established within the atherosclerotic plaques [13].

While other studies, which have been carried on showed that PCSK9 concentration was associated with atherosclerotic necrotic core independent on LDL-c level. In most recent studies, it was found that in patients with ischemic heart disease, lipopolysaccharides related inflammation induce PCSK9 expression by decreasing PPAR-a and PCSK9 inhibitors farnesoid X receptors.

Concerning RBP4, the study showed that statins group had a lower RBP4 when compared to non-statins. The role of statins therapy on RBP4 in patients is controversial and several studies on the metabolic effect of RBP4 were carried on.

A previous study conducted that statins reduced the activity of RBP4 indirectly by decreasing the level of intestinal microsomal triglyceride transfer protein MTP, since RBP4 exhibited part of its dyslipidemic effect via activation of MTP protein [14].

In contrast Wanders and coworkers showed that RBP4 concentration was unchanged in patients on statins therapy. RBP4, mainly formed in the liver and visceral adipose tissue, and statins showed indirect effect on RBP4 by attenuating adipocyte maturation and glucose transporter 4 (GLUT4) expression via inhibiting isoprenoid biosynthesis , and thus affecting RBP4 [2].

Furthermore, the study displayed lower level of CRP in statins group in comparison to non-statins group and controls. CRP plays an important role in the pathogenesis of atherosclerosis, especially by increasing macrophages

uptake of oxidized LDL, induces the expression of endothelial cell adhesion molecules, weakens the production of nitric oxide, and enhances the production of tissue factors [15].Sushant and coworkers [16] showed a reduction in CRP level on regular statins therapy , through different mechanisms including; reduce hepatic productions of CRP via reducing IL-6, exerts anti-inflammatory effect by impair binding of lymphocytes to intracellular adhesion molecules-1 (ICAM-1), and down regulates the prenylation activities via inhibiting the mevalonate pathway.

Comparative effect between atorvastatin & rosuvastatin on adipocytokine and inflammatory biomarkers.

PCSK9 serum level had an overall significant difference between atorvastatin and rosuvastatin; rosuvastatin had higher PCSK9 value than atorvastatin. Several previous studies regarding the effect of lipid lowering therapy on PCSK9 level revealed that the majority of statins cause an increase in PCSK9 to a various level depending on the dose, type and duration of statins. Statins cause inhibition of intracellular cholesterol synthesis, and thus inducing upregulation of LDL-R and PCSK9 expression in order to restore cholesterol, so statins have a paradoxical effect. Evidence showed that even single dose statins may result in increasing PCSK9 level through direct activation of SREBP-2. A previous study highlight the impact of dose and duration of statins and showed that 10 mg of atorvastatin not cause a significant increase in PCSK9 level while 20 mg atorvastatin increased PCSK9 by 35 % following 4-6 months.

The current study is in agreement with a previous study which has shown that administration of 40 mg atorvastatin resulted in 34% increase in PCSK9 level while 20 mg of rosuvastatin caused an increase to about 28% in male and 35% in female [17]. In contrast, a recent study showed that the elevation in PCSK9 level was greater in lipophilic statins (atorvastatin , pitavastatins , simvastatins , fluvastatins) as compared to hydrophilic statins (rosuvastatin and pravastatins) [18] .

The study also obtained that there was no substantial difference between both rosuvastatin and atorvastatin using patients in regard to RBP4, but patients on atorvastatin showed lower level of RBP4.The dose, duration and sample size may all affect our results. Even though, the information about the individual effect of statins on RBP4 is little, a previous study demonstrated that lipid lowering therapy and particularly atorvastatin can ameliorate inflammatory and adipocytokine mediators in visceral adipose tissue, this may be, in part, due to its pleiotropic effect [19]. Moreover, rosuvastatin showed reduction in adipocyte size and altered the distribution of fat in visceral adipose tissue as reported by Neto-Ferreira [20], which is considered as important source of RBP4.

Furthermore, the present study showed lower level of CRP in patients with rosuvastatin as compared to atorvastatin, however it was not statistically significant and this may be due to small sample size of patients. CRP had the greatest attention among numerous inflammatory biomarkers owing to its ability to predict the response to statins therapy. A previous study reported that rosuvastatin reduced CRP to a greater extent than the same dose of atorvastatin [21]. Similarly another study showed the effect of statins on CRP in patients has been displayed that rosuvastatin 20 mg is more effective in reducing circulating CRP level in comparison to atorvastatin 40 mg, within 4 weeks of statins therapy [22, 23].

5. Conclusions

Statins showed a paradoxical effect by causing a reduction in LDL-c and at the same time it enhanced PCSK9 level, with a greater elevation in PCSK9 was observed in rosuvastatin treated patients in comparison to atorvastatin. Statins therapy had a protective effect in lowering RBP4. Although there was no significant difference between rosuvastatin and atorvastatin using patients in regard to RBP4, patients on atorvastatin showed a lower mean level of RBP4. Rosuvastatin showed best anti-inflammatory effect by reducing CRP than atorvastatin in patients with ACS.

Conflicts of interest

There are no potential conflicts of interest.

Funding and sponsorship

Nil

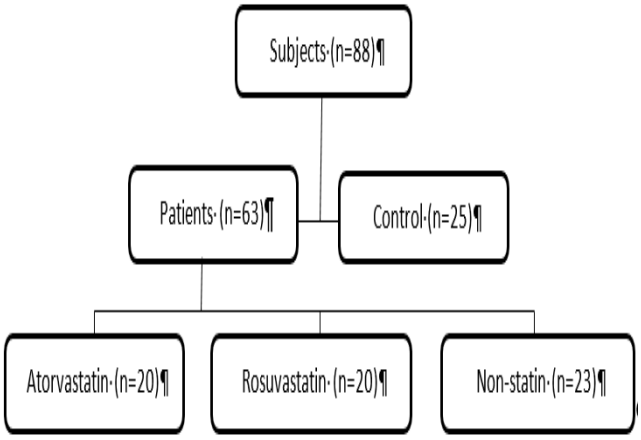

Figure .1 consort flow diagram of the present study

Table 2: Patients' metabolic profiles in relation to statin medication

Variables	Controls(n=25)	Statins (n=40)	Non –statins (n=23)	P
TC (mg/dl)	160.4±30.7	141.87±40.67	205.78±40.6 # ¤	**0.001**
HDL-c (mg/dl)	29.5±5.4	33.4±9.09*	27.4±3.96 # ¤	**0.005**
TG (mg/dl)	91.8±44.66	133.57±37.93 *	160.65±39.9# ¤	**0.001**
VLDL(mg/dl)	18.37± 8.93	26.71±7.58*	32.13±7.98 # ¤	**0.001**
LDL-c(mg/dl)	112.46±32.69	81.76±42.42*	146.17±40.69 # ¤	**0.001**

Data are presented as mean ± SD, ANOVA test and LSD post-hoc test, TC: total cholesterol , TG: triglyceride , HDL: high density lipoprotein , LDL: low density lipoprotein , VLDL : very low density lipoprotein
*** P<0.05 compared between control with statin groups**
 # P<0.05 compared between statin with non-statin groups
¤ P<0.05 compared between controls with non-statin groups

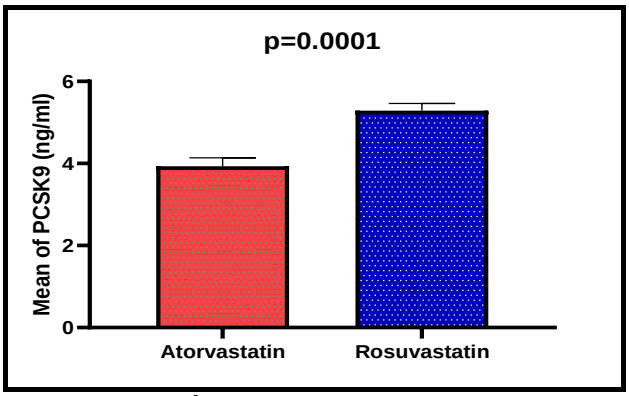

Figure 2 Mean of PCSK9 in Atorvastatin vs. Rosuvastatin

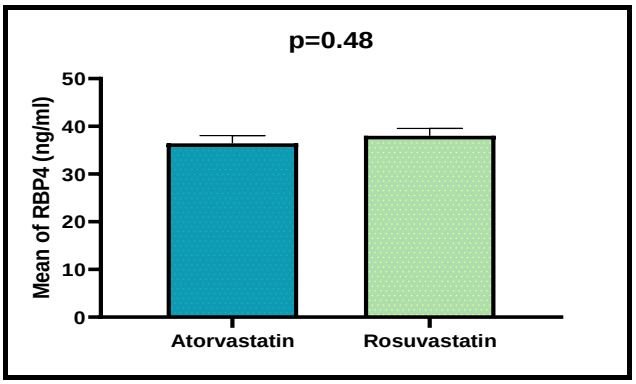

Figure 3 Mean of RBP4 in Atorvastatin vs. Rosuvastatin

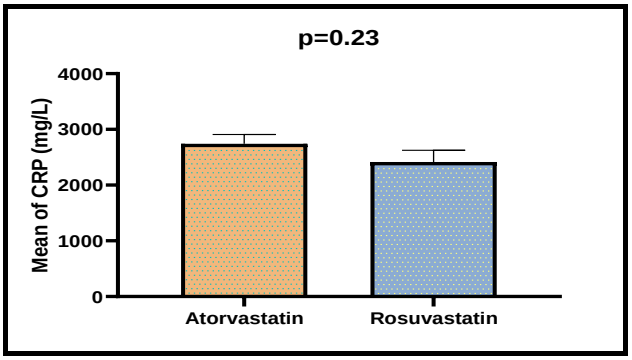

Figure 4 Mean of CRP in Atorvastatin vs. Rosuvastatin

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