Efficacy of atorvastatin in treatment of Iraqi obese patients with hypercholesterolemia

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ABSTRACT

Background: dyslipidemia plays a crucial rule in the development of cardiovascular disease, which has become the leading cause of death in most developed countries as well as in developing countries [(1).] The effects of reducing low density lipoprotein – C (LDL-C) concentrations on the prevention of cardiovascular events and stroke have been well reported in many clinical trials.

Objectives: Evidence supports the use of statins for lipid modifications in the primary prevention of coronary artery disease, morbidity and mortality. This study aims to determine the effectiveness of atorvastatin in treating dyslipidemia in Iraqi obese patients.

Methods: 200 overweight and obese patients with hypercholesterolemia, according to NCEP ATP III criteria, were included. They were randomized into 3 groups according to atorvastatin dose, 10, 20, 40 mg/ day, and treated for 8 weeks. Blood lipid profile, liver enzymes ALT and AST, urea, creatinine, uric acid, calcium and glucose were measured before and after therapy.

Results: There was a significant reduction of total cholesterol (TC), Triglycerides (TG), low density lipoprotein (LDL), very low density lipoprotein (VLDL), but a non-significant reduction of high density lipoprotein (HDL) with all atorvastatin doses. The high doses of the drug caused a significant elevation of serum levels of ALT and AST and a significant decrease of blood calcium; but there was no significant change in blood levels of urea, creatinine, uric acid or glucose with any dose.

Conclusion: Short-term atorvastatin therapy in dyslipidemic obese patients caused a reduction of TC, TG, LDL, and VLDL, but had no significant effect on HDL, non-significant changes in blood urea, serum creatinine, serum uric acid or blood glucose, while there was a dose dependent elevation of ALT and AST.

Key word: Atorvastatin,hypercholesterolemia, Iraqi obese patients.

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Dyslipidemia plays a crucial rule in the development of cardiovascular disease, which has become the leading cause of death in most developed countries as well as in developing countries [1]. The effects of reducing low density lipoprotein – C (LDL-C) concentrations on the prevention of cardiovascular events and stroke have been well reported in many clinical trials [2]. Studies have reported that decreasing plasma LDL-C concentrations using 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) was associated with significantly reduced risks for cardiovascular mortality, morbidity, and coronary artery disease events [3]. It has been reported that there was a positive association between body mass index (BMI) and serum cholesterol level [4]. In addition, the National Health and Nutrition Examination Survey (NHANES) III data has described an association between obesity, the prevalence of high blood pressure and high blood cholesterol levels [5].

In Iraq, the prevalence of high serum cholesterol (≥ 5.2 mmol / L) was 37.5% being higher among males than females (38.9% Vs 36.5% respectively). In both sexes the rate increased with increasing age. Overweight was estimated to be 66.9%, and obesity constituted one third of the population being higher among females (38.2%) as compared to males (26.2%) [6]. On the basis of observational data, the causal association between dyslipidemia and increased rates of cerebrovascular disease was unclear, but trial evidence has shown notable reductions in stroke rates with statin use [7]. A series of large randomized endpoint trials has established the benefits of statins for the prevention of major fatal and non-fatal cardiovascular events. These data were consistent with experimental, observational and other trial data in establishing dyslipidemia as a major independent risk factor for coronary heart disease [8].

Elevated plasma triglyceride concentrations contribute to increased risk of cardiovascular disease, both directly and because such elevations “keep bad company” with associated risk factors such as obesity, metabolic syndrome, pro-inflammatory and pro-thrombotic biomarkers, and type 2 diabetes mellitus [9]. It was found that patients with primary hypertriglyceridemia have an elevated turnover rate of non-esterified fatty acids; this elevation occurred independently of body fat content and abdominal obesity [10]. It was found that women with abdominal obesity had much higher non-esterified fatty acid concentrations due to higher non-esterified fatty acid output by adipose tissue [11]. Patients that had elevated secretion of non-esterified fatty acids, whether due to excess adipose tissue (obesity), abnormal fat distribution (abdominal obesity), or a primary insulin resistance in adipose tissue, they would have an elevated level of non-esterified fatty acids in the plasma. Excess non-esterified fatty acids overloaded a variety of different tissues in the body with lipid and apparently alteredcellular processes predisposing patients to the metabolic syndrome.

In this study we aimed at assessing the efficacy and tolerability of atorvastatin during the treatment of hypercholesterolemia in obese patients.

Methods. Study design: Open-label, prospective nonrandomized (before-after treatment) interventional study. Ethical approval was obtained from ethical and scientific committee of AL-KindyCollege of Medicine. The study was conducted at Obesity Research and Therapy Center / AL-KindyCollege of Medicine.

Inclusion criteria: 200 patients were included in the study and they were divided into the following groups:1. Both genders were overweight or obese (BMI 25 kg/ m^2 plus) and aged 20-70 years. 2. Patients to be lipid-lowering drug naïve. 3. Patients had a fasting triglyceride concentration < 400 mg/ dL and an LDL-C concentration ≥ 160 mg/ dL or ≥ 130 if they had 2 or more cardiovascular risk factors or ≥ 100 if they were diabetic and their LDL was ≤ 300 mg/ dL.

Study endpoint: 200 patients to complete 8 weeks of therapy.

Exclusion Criteria: 1. Hypersensitivity to statins (HMG-CoA Reductase inhibitor). 2. Rhabdomylosis or muscle enzymes (SGOT, SGPT) elevation ≥ 2 folds above the upper normal limit. 3. Acute liver disease or hepatic dysfunction. *4.* Elevated serum creatinine (≥ 2.5 mg/ dL). 5. Uncontrolled hypertension (resting systolic blood pressure ≥ 160 mmHg and diastolic ≥ 100 mmHg with antihypertensive treatment). 6. Patients with potential adherence failure, including those with psychiatric or psychological conditions that could impair their ability to follow protocol instructions. 7. Pregnancy, breastfeeding women and women of childbearing potential that required contraception throughout the study.

Withdrawal Criteria: 1. Development of a hypersensitivity reaction and/or an adverse reaction that necessitated treatment withdrawal. 2. Protocol scheduled visits violation. 3. Patient's desire to quit.

Intervention and follow up: On the screening day (-24 hours) patients underwent a complete physical examination, with medical history and laboratory assessments. Patients meeting the selection criteria were recruited into the study. Dietary information was explained and atorvastatin calcium was prescribed for a period of 8 weeks starting on day 0 after the patient's consent form was signed.

Atorvastatin dose and LDL-C goals were established according to physician's decision according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [(12).] Patients were divided into three groups: atorvastatin (Lipigard Julphar) 10mg/day, atorvastatin 20mg/day and atorvastatin 40mg/day. No dose changes were attempted during the study period.

The patients' visits were scheduled at 4 week intervals and medication was prescribed and supplied at each scheduled visit. At the end of week 8 the study ended and final assessments of laboratory profile. Grapefruit juice was advised to be avoided as it might increase plasma concentrations of atorvastatin.

Tolerability was assessed through objective measurements of renal and liver functions, including ALT, AST, blood urea and serum creatinine, and through measurements of fasting blood sugar (FBG) serum uric acid and serum calcium. Symptoms related to side effect of the drug were registered and considered, but they were not included in the study statistics.

Laboratory assessment: All blood samples were drawn after a minimum 12-hour fasting period. Blood pressure was measured in the morning. 2 blood pressure readings were taken with the patient in the sitting position after a 5-minute rest. Lipid profile tests including triglyceride (TG), total cholesterol, LDL-C, high density lipoprotein-C (HDL-C) and very low density lipoprotein (VLDL); and blood biochemistry tests including urea nitrogen, creatinine, glucose, SGOT, SGPT, uric acid and calcium were performed on the screening day and 8 weeks later.

End points included the mean of difference percent change from baseline to week 8 in LDL-C, total cholesterol, TG, VLDL and HDL-C. Vital signs, adverse events, and laboratory data were reviewed and medically assessed by the investigator at each scheduled visit. The investigator or his/her designee were available within the clinical facility and would ask the patient for his/her wellbeing at the time of clinical examination and at the time of recording of vital signs.

Statistical analysis: All data were analyzed by intention to treat. Because patients were randomized, baseline values were not statistically tested between treatment groups. Means and standard deviations (SD) were measured before and after intervention for each group. Paired t test was used to find the significant differences. P value less than 0.05 was considered statistically significant.

Results. Two hundred fifty three patients were recruited; only 200 completed the study, because of protocol scheduled visits violation. No quitting due to hypersensitivity or side effect or patient desire. Female to male ratio was 8: 2.

Mean age of all patients was 45.49 years (± 11.19), of males was 44.15 years (± 10.45) and of females was 45.83 years (± 11.38) with no gender significant difference (P = 0.39) (Table 1).The mean (± SD) BMI of all patients was 39.79 kg/ m2 (± 7.17), of males was 38.89 kg/ m2 (± 7.38) and of females was 40.02 kg/ m2 (± 7.12) with no significant gender difference (P = 0.39). 35% of the patients had diabetes mellitus and 30% had hypertension with no significant gender difference as seen in Table 1. Total cholesterol level decreased highly significantly (P < 0.0001) in all atorvastatin dose groups after 8 weeks of treatment, Table 2.

Serum TG decreased significantly (P < 0.001) in group atorvastatin 10 mg/ day, and highly significantly (P < 0.0001) in groups atorvastatin 20 mg/ day and 40mg/ day, after 8 weeks of treatment,Table 3.

LDL-C level decreased highly significantly (P < 0.0001) in all atorvastatin dose groups after 8 weeks of treatment, Table 4. There was a non-significant change in serum level of HDL in all atorvastatin dose groups, Table 5. VLDL decreased highly significantly (P < 0.0001) in the groups atorvastatin 20 mg/ day and 40 mg/ day, after 8 weeks of treatment, Table 6.

There was a significant increase in the level of liver enzyme ALT with atorvastatin 40 mg/ day dose group, and in AST with atorvastatin dose groups 20 mg/ day and 40 mg/ day, Table 7, Table 8. There was no significant change in blood urea and creatinine levels for any of atorvastatin dose groups, Table 9, Table 10.

Blood calcium level showed a significant decrease with 40 mg/ day atorvastatin dose, after 8 weeks of therapy, but no significant changes with the other doses, Table 11. There was no significant change in blood uric acid or glucose levels for any of atorvastatin dose groups, Table 12, Table 13.

Discussion. Among adults, obesity prevalence increased from 13% to 32% between the 1960s and 2004. Currently in USA, 66% of adults are overweight or obese [13]. In Iraq and according to STEP study done in 2006, 38.2% of Iraqi females aged 25-65 years were obese, a rate that was higher than in Iraqi males; in addition, overweight and obesity was found to be higher in the age group 45-65 years with mean BMI being 30.2 kg/ m^2 [6]. In the current study, females composed 80% of the recruited patients a percent that was more than was usually encountered in other studies. This can be explained that female attained obesity clinic more frequently than male due to social, asthetic or

Table 1: Criteria of patients recruited to the study.

Criteria		Female (n = 160)	Male (n = 40)	Total (n = 200)	P value
Age (Years)	Mean ± SD	45.83 ± 11.38	44.15 ± 10.45	45.49 ± 11.19	0.3973
BMI (Kg / m^2)	Mean ± SD	40.02 ± 7.12	38.89 ± 7.38	39.79 ± 7.17	0.3739
Diabetes Mellitus No Yes	No (%)	107 (82.3%) 53 (75.7%)	23 (17.7%) 17 (24.3%)	130 70	0.266
Hypertension No Yes	No (%)	110 (79.1%) 50 (81.9%)	29 (20.9%) 11 (18.1%)	139 61	0.645

Table 2: Effect of atorvastatin on total serum cholesterol level.

Doses	Cholesterol (mg/dl)			P value
		Before	After	
10 mg (n = 48)	Mean ± SD	230.29 ± 24.21	196.33 ± 34.28	0.0001
20 mg (n = 69)	Mean ± SD	243.45 ± 36.87	196.74 ± 36.69	0.0001
40 mg (n = 83)	Mean ± SD	270.23 ± 37.95	213.16 ± 38.55	0.0001

Table 3: Effect of atorvastatin on serum triglycerides (TG) level.

Dose		TG (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	193.13 ± 48.64	173.04 ± 46.59	0.0415
20 mg (n = 69)	Mean ± SD	191.96 ± 53.93	160.64 ± 45.55	0.0003
40 mg (n = 83)	Mean ± SD	205.57 ± 56.97	178.45 ± 46.58	0.0010

Table 4: Effect of atorvastatin on low density lipoprotein (LDL) level.

Dose		LDL (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	144.90 ± 24.46	118.92 ± 23.28	0.0001
20 mg (n = 69)	Mean ± SD	157.30 ± 31.32	119.35 ± 29.31	0.0001
40 mg (n = 83)	Mean ± SD	184.76 ± 32.04	134.46 ± 30.04	0.0001

Table 5.: Effect of atorvastatin on high density lipoprotein (HDL) level.

Dose		HDL (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	47.56 ± 14.77	45.49 ± 11.55	0.4463
20 mg (n = 69)	Mean ± SD	47.45 ± 14.68	45.77 ± 8.01	0.4055
40 mg (n = 83)	Mean ± SD	47.23 ± 8.46	45.43 ± 7.36	0.1455

Table 6: Effect of atorvastatin on very low density lipoprotein (VLDL) level.

Dose		VLDL (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	39.25 ± 11.06	34.35 ± 9.21	0.0204
20 mg (n = 69)	Mean ± SD	40.25 ± 12.52	31.97 ± 8.98	0.0001
40 mg (n = 83)	Mean ± SD	42.12 ± 13.38	34.88 ± 9.94	0.0001

Table 7: Effect of atorvastatin on serum ALT level.

Dose		ALT (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	30.35 ± 12.78	29.19 ± 10.61	0.6296
20 mg (n =69)	Mean ± SD	29.51 ± 12.95	33.39 ± 11.70	0.0670
40 mg (n = 83)	Mean ± SD	28.73 ± 12.13	33.58 ± 13.01	0.0140

Table 8: Effect of atorvastatin on serum AST level.

Dose		AST (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	26.65 ± 10.17	29.65 ± 10.55	0.1594
20 mg (n = 69)	Mean ± SD	26.26 ± 9.59	30.49 ± 10.81	0.0163
40 mg (n = 83)	Mean ± SD	28.16 ± 11.84	32.63 ± 12.53	0.0193

Table 9: Effect of atorvastatin on blood urea level.

Dose		Urea (mg/dl)		P value
		Before	After	
10 mg (n =48)	Mean ± SD	29.69 ± 7.19	29.42 ± 6.18	0.8440
20 mg (n = 69)	Mean ± SD	30 ± 8.39	29.70 ± 7.22	0.8222
40 mg (n = 83)	Mean ± SD	30.27 ± 9.65	29.83 ± 6.45	0.7303

Table 10: Effect of atorvastatin on serum creatinine level.

Dose		Creatinine (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	0.69 ± 0.21	0.68 ± 0.20	0.8117
20 mg (n = 69)	Mean ± SD	0.69 ± 0.19	0.67 ± 0.17	0.7563
40 mg (n = 83)	Mean ± SD	0.82 ± 0.05	0.98 ± 0.31	0.3865

Table 11: Effect of atorvastatin on serum calcium level.

Dose		Calcium (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	9.21 ± 1.14	9.25 ± 0.62	0.8314
20 mg (n = 69)	Mean ± SD	9.23 ± 0.94	9.04 ± 0.89	0.2249
40 mg (n = 83)	Mean ± SD	9.50 ± 1.09	9.07 ± 0.99	0.0086

Table 12.: Effect of atorvastatin on serum uric acid level.

Dose		Uric acid (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	5.38 ± 1.21	5.14 ± 1.13	0.3178
20 mg (n = 69)	Mean ± SD	5.31 ± 1.34	5.06 ± 1.08	0.2297
40 mg (n = 83)	Mean ± SD	5.39 ± 1.55	5.07 ± 1.28	0.1489

Table 13: Effect of atorvastatin on fasting blood glucose.

Dose		Glucose (mg/dl)		P value
		Before	After	
10 mg (n = 48)	Mean ± SD	110.98 ± 31.61	107.81 ± 21.06	0.5645
20 mg (n = 69)	Mean ± SD	119.84 ± 32.63	111.90 ± 31.25	0.1467
40 mg (n = 83)	Mean ± SD	120.67 ± 31.79	118.54 ± 32.13	0.6682

medical reasons.

In one study, it was shown that obese subjects had significant dyslipidemia, 37% of them had total cholesterol > 200 mg/ dl, 46% had HDL cholesterol <40 mg/ dl, 31% had LDL cholesterol >130 mg/ dl and 51% had TG >150 mg/ dl [14], while 37.2% of Iraqis had hypercholesterolemia [6].

Novel lipid dependent metabolic risk factors associated with obesity were the presence of the small dense LDL phenotype, postprandial hyperlipidemia with accumulation of atherogenic remnants and hepatic overproduction of apoB-containing lipoproteins. All these lipid abnormalities were typical features of the metabolic syndrome and might be associated with a pro-inflammatory gradient which in part might originate in the adipose tissue itself and directly affected the endothelium [15].

Atorvastatin appeared to reduce total cholesterol, LDL-C, TG concentrations, and apo-B to a greater extent than currently available hydroxyl methyl glutarate co enzyme A (HMG-Co) reductase inhibitors [16]. Atorvastatin would achieve a good effective control in the management of hypercholesterolemic patients with or without coronary heart disease and risk factors [17]. The results of our study showed highly significant reduction in total cholesterol and LDL cholesterol levels with atorvastatin therapy, especially with the higher doses, findings that were in agreement with most other studies.

The results of the current study showed a highly significant, dose-dependent reduction in fasting TG levels after 8 week treatment with atorvastatin. This effect could be attributed to improvement of postprandial lipemia after treatment with atorvastatin as has been shown in animal models, in healthy subjects, and in patients with combined hyperlipidemia [18].

Likewise, atorvastatin caused a significant decrease in fasting VLDL levels in this study. This effect can be explained that atorvastatin caused improvement of dyslipoproteinemia by increasing the catabolism of VLDL, intermediate density lipoprotein (IDL), and LDL apo-B without significantly altering synthesis or turnover of HDL apo-AI [19].

This study showed no significant effect of atorvastatin on fasting HDL level with any of the used doses. This finding is inconsistent with other studies. On the other side atorvastatin at a daily dose of 10 to 80 mg has been associated with progressively decreasing rises in the levels of HDL as the dose increases (negative dose response), an effect not reported with other statins [20], with the higher dose of atorvastatin producing a smaller increase in HDL than did the lower dose [21]. Another study showed that all doses of atorvastatin significantly increased HDL-C levels [22]. A similar finding to ours was recognized by Robinson and colleagues who stated that increasing age and abdominal obesity and lowering baseline high sensitivity C reactive protein (hs-CRP) were significant predictors of greater reductions in LDL-C, non-HDL-C, apolipoprotein-B, total cholesterol, TG and VLDL cholesterol but not for changes in HDL-C [23]. The absolute increase in HDL cholesterol was influenced by the decrease in plasma TG levels, BMI and alcohol intake [24].

The risk of statin-associated elevation of liver enzymes, or rhabdomyolysis, was not related to the magnitude of LDL-C reduction [25]. The asymptomatic elevation in transaminases, after taking statins and generally occurring in the first months of treatment, were reversible and they returned to normal on stopping statin treatment, with dose reduction, or even spontaneously with continuation of the same statin dosage [26]. It has been questioned whether the effect on transaminases indicated hepatotoxicity or just a hepatic reaction to a greater reduction in lipid levels as all lipid-lowering drugs might increase liver enzymes [27]. In this study, although the treatment duration was short, no patient showed clear features of hepatitis, but there was significant elevation of ALT with 40 mg/ day atorvastatin, and significant AST elevation with 20 and 40 mg/ day atorvastatin, effects that were apparently dose dependent.

In untreated dyslipidemia in patients with coronary heart disease and normal renal function at baseline, creatinine clearance declined over a period of three years. Statin treatment prevented this decline and significantly improved renal function, potentially offsetting an additional factor associated with coronary heart disease risk [28]. Moreover, heart protection study subgroup analysis for participants with diabetes mellitus showed that unadjusted serum creatinine concentrations increased in all patients, with or without diabetes mellitus, over a period of 4.6 years. However, allocation to statin significantly decreased the rise in serum creatinine values in patients with and without diabetes mellitus [29].

Atorvastatin and rousovastatin showed similar renal protective effects in patients at high cardiovascular risk with comparable rates of new onset proteinuria when commonly used doses were considered. In patients with chronic kidney disease, no further deterioration of glomerular filtration rate was observed [30]. In the current study, there was no significant negative effect of short term atorvastatin therapy on renal function, as shown by the blood urea and serum creatinine levels before and after treatment.

Calcium elevation may be a crucial event for myotoxicity induced by atorvastatin [31]. Atorvastatin increased vitamin D levels, an increase that could explain some of the beneficial effects of the drug at the cardiovascular level and not due to cholesterol levels [32]. In the current study, there was no significant elevation of calcium; instead there was a significant decline of calcium with 40 mg/ day atorvastatin dose, possibly due to associated dieting. On the other hand and in contrast to some previous data, rosuvastatin and aatorvastatin, two potent and widely prescribed statins, did not cause significant changes in 25-hydroxyvitamin D levels [33].

Milionis stated that atorvastatin significantly lowered serum uric acid levels and this was in favor of a preferable choice of atorvastatin for the treatment of hyperuricemia [34]. Atorvastatin significantly reduced serum uric acid levels in patients with coronary heart disease, thus offsetting an additional risk factor in these patients [22]. But the mild decline in serum uric acid level in the current study was insignificant possibly due to short term therapy.

In the general population, statins did not seem to have critical adverse effects on glucose tolerance but they might modify the natural course of development of diabetes in certain patients [35]. In one report, 220 patients with hypercholesterolemia were treated either with a placebo or with different doses of atorvastatin and were followed up for a period of 2 months only; those receiving the highest dose developed greater insulin resistance, higher insulin levels, and higher hemoglobin A1c levels compared with those receiving the lowest dose or placebo [36]. Atorvastatin impaired glucose tolerance by attenuating adipocyte maturation and SLC2A4 expression and by inhibiting isoprenoid biosynthesis, actions of atorvastatin that could potentially affect the control of type-2 diabetes [37]. Yet the present study showed no significant effect of atorvastatin on the mean fasting glucose level, although,it was higher than normal, an effect that might be due to the associated dieting in an attempt to reduce weight.

In conclusions, Short term therapy with atorvastatin in obese patients decreased total cholesterol, TG, LDL, and VLDL, but had no significant effect on HDL, blood urea, serum creatinine, serum uric acid or blood glucose. There was a dose dependent elevation of liver enzymes ALT and AST, together with a significant decrease in serum calcium with the high dose treatment.

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