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Effectiveness of Atorvastatin in Treatment of Obese Patients with Dyslipidaemia

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Abstract **Original Research Article**

Background: Numerous comorbidities, such as type 2 diabetes mellitus, hypertension, dyslipidemia, and cardiovascular (CV) disease are all made more likely by obesity. A higher mortality rate in the general population is strongly correlated with a high body mass index (BMI). In patients who are at high risk of experiencing an atherosclerotic CV event, the use of statins lowers mortality and recurrent adverse cardiac events across a broad range of cholesterol levels. Therefore, statin therapy is advised for secondary prevention in all high-risk patients, including those with obesity. ***Objectives***: There is evidence to support the primary prevention of coronary artery disease, morbidity, and mortality using statins for lipid modifications. The purpose of this study is to ascertain the immediate impact of atorvastatin on the lipid profile in obese Jordanian patients. ***Methods***: According to NCEP ATP III criteria, 200 overweight and obese patients with hypercholesterolemia were included. They received treatment for 2 months after being randomly divided into 3 groups based on the dosage of atorvastatin: 10, 20, and 40 mg/day. ***Results***: With all atorvastatin doses, there was a significant desirable increase in high-density lipoprotein (HDL), and significant reduction in total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), and very low-density lipoprotein (VLDL). ***Conclusion***: In dyslipidemic obese patients, short-term atorvastatin therapy resulted in lower levels of TC, TG, LDL, and VLDL as well as a desirable increase in HDL.

Keywords: Atorvastatin, hyperlipdemia, obesity.

INTRODUCTION

Cardiovascular disease (CVD) continues to be a leading factor in early mortality and rising medical expenses. The main causes of CVD include cardiometabolic, behavioral, environmental, and social risk factors CVD is primarily influenced by cardiometabolic, behavioral, environmental, and social risk factors [1]. In order to direct public policy and serve as a benchmark for decision makers, a systematic, comparable, and consistent analysis of long-term trends and patterns in global CVD is required. Ischemic heart disease (IHD) and stroke, both clinical manifestations of atherosclerosis, account for 85% of deaths from CVD [2]. The leading cause of death for both men and women in USA and, in fact, the entire world is atherosclerotic coronary heart disease. Atherosclerosis is the main contributing factor to coronary artery disease (CAD), which manifests as atherosclerotic changes within the walls of the coronary arteries [3].

Production of steroid hormones, formation of bile acids, or producing energy require lipids like cholesterol or triglycerides to be absorbed from the intestines and transported all over the body by lipoproteins. Triglycerides, high-density lipoprotein, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL) and cholesterol are major contributors to these pathways. Dyslipidemia can result from an imbalance of any of these elements, whether due to organic or inorganic factors [4]. According to the Global Burden of Disease study from 2016, high levels of total cholesterol were responsible for 94% of all disability-adjusted life years (DALYs) and approximately 4.5 million deaths in 2016. The World Health Organization (WHO) reports that in adults over 25 years of age, elevated plasma levels of TC were prevalent globally in 2008 at 40 %, and elevated plasma LDL-C levels were responsible for more than one-third of CVD-related mortality [5].

Rapid urbanization, socioeconomic advancement, longer lifespans, unbalanced diets, and lifestyle modifications have all recently contributed to a higher rate of CVD in the Middle Eastern population, including Jordan. According to a recent study from Jordan, the prevalence of dyslipidemia's hypercholesterolemia and hypertriglyceridemia increased by nearly doubling from 23.3% and 24.1% in 1994 to 44.7% and 42.1%, respectively, in 2017 [6].

Public health organizations around the world have concentrated on lowering modifiable CVD risk factors, such as hypertension (HTN), an unhealthy diet, obesity, and dyslipidemia to face the rising prevalence of CVD and its risk factors, A diet high in fat and calories can result in dyslipidemia, which can then lead to endothelial dysfunction [7]. The ratios of serum TG, TC, LDL, HDL, TC/HDL, and LDL/HDL are independent predictors of the risk of CVD. Currently, lowering serum LDL-C levels is the main goal in the management of dyslipidemia [8]. It is difficult to understand how lipids and stroke are related. There is a direct correlation between cholesterol levels and ischemic stroke in the majority of epidemiological cohorts. Higher total and LDL cholesterol levels are linked to a higher risk of having an ischemic stroke in most observational studies, but not all of them [9]. Statins termed also 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors have shown efficacy in lowering the risk of stroke in addition to their cardiovascular advantages. Several statins have been linked to stroke risk reductions ranging from 12–42% in primary stroke prevention trials [10].

Numerous epidemiological studies, including a number of genetically based analyses, have shown that triglycerides are related to cardiovascular risk independently of LDL-C, and this has prompted the development of a number of new therapeutic drugs that are intended to lower plasma triglycerides [11]. According to the triglyceride hypothesis, higher plasma triglyceride levels are associated with a higher risk of cardiovascular disease, while lower levels are associated with a lower risk [12]. It was discovered that excessive intra-abdominal adipose tissue accumulation, also known as visceral obesity, is a phenotype associated with ectopic triglyceride storage, dysfunctional subcutaneous adipose tissue expansion, and clustering cardiometabolic risk factors [13]. In the same vein, after menopause, women are more susceptible to the putative link between excessive abdominal adiposity and insulin resistance because older age is linked to increased abdominal fat deposition and the redistribution of fat from subcutaneous to visceral abdominal depots as a result of attenuated secretions of lipid-mobilizing sex steroid hormones. Increased adipose tissue mass is thought to be the cause of elevated NEFA concentrations in obesity [14].

In this study we aimed at evaluating the effectiveness of atorvastatin in treatment of obese patients with dyslipidaemia.

METHODOLOGY

Study Design

This was a prospective open label non-randomized study performed in King Medical (KHMC) at The Royal Medical Services (RMS) in Amman/Jordan from August 2022 to October 2022. This study was approved by the ethical committee of RMS. Two hundred participants were enrolled in this study. Participants were divided into three subgroups (group A, group B, and group C): according to Atorvastatin dose, 10, 20, 40 mg/ day respectively, and treated for 2 months. Adult Jordanians (18-70 years old, male or female) who were overweight or obese (BMI 25 kg/m2 or greater), had never taken a lipid-lowering medication, had fasting triglyceride concentrations above 400 mg/dL and LDL-C concentrations below 160 mg/dL, or had 130 mg/dL if they had two or more cardiovascular risk factors, or 100 mg/dL if they had diabetes and their LDL was below 300 mg/dL, were included in the study. while the exclusion criteria include patients with one or more of the following:

1. Who were non-Jordanian,
2. Clinical evidence of other autoimmune or life-threatening disease,
3. Hypersensitivity to statins.
4. Suffering from acute liver disease, hepatic dysfunction, or chronic kidney disease.
5. Uncontrolled hypertension.
6. Patients with psychological conditions.
7. Pregnancy or breastfeeding women.

Intervention and follow up

Patients underwent a thorough physical examination, a medical history review, and laboratory evaluations on the screening day (within 24 hours). Patients who fit the criteria for enrolment in the study were chosen. Following the patient's consent to participate in the study, dietary instructions were given, and atorvastatin (Atorvast®)/JOSWE was prescribed for an 8-week duration beginning on day 0 of the study. The dosage of atorvastatin (Atorvast®) and LDL-C targets were decided upon by a physician in accordance with NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) recommendations. Atorvastatin 10 mg, Atorvastatin 20 mg, and Atorvastatin 40 mg were given to the patients in three different groups.

The patients' appointments were scheduled every four weeks, and at each appointment, medication was prescribed and given out. Final evaluations of the laboratory profile and the study were completed at the end of week 8.

Laboratory Analysis

A minimum 12-hour fasting period was followed in the collection of all blood samples. triglyceride (TG), total cholesterol, LDL-C, high density lipoprotein-C (HDL-C), and very low-density lipoprotein (VLDL) tests are included in lipid profiles.

Endpoints included in the study were the increase or decrease in LDL-C, total cholesterol, TG, VLDL, and HDL-C from week 8 to week 4 of the study. At each scheduled visit, the medical doctor (MD) reviewed and evaluated the patient's vital signs, side effects, and laboratory results from a medical standpoint.

Statistical Analysis

For each group, the means and standard deviations (SD) were calculated before and after the intervention. The significant differences were discovered using the paired t test. A *p*-value of 0.05 or less was regarded as statistically significant.

RESULTS

The mean age of total three groups was 55.9±11.11 years. In addition, the mean weight of whole patients was 73.19±13.85 Kg while the average weight of the control group was 69.2±14.82 Kg. Other demographic and clinical characteristics showed that there was no gender significant difference among demographic variables (P >0.05) (Table 1).

Table 1: Demographic Characteristics of the Participants

Variable	group a N=65	group b N=75	GROUP C N=60	TOTAL N=200	P VALUE
	Mean ±SD				
Age	57.1±11.20	52.9±11.39	56.9±11.19	55.9±11.11	0.276
BMI	41.02 ± 7.14	42.13 ± 7.33	41.32 ± 7.45	41.21±7.7	0.323
Sex {N (%)}					
Male	36 (56.4)	32 (42.6)	33 (55)	101 (50.5)	0.156
Female	29 (43.6)	43 (57.4)	27 (45)	99 (49.5)	0.214
Marital status {N (%)}					
Married	62 (95.3)	69 (92)	55 (91.6)	186 (93)	0.376
Separated	0 (0)	0 (0)	0 (0)	0 (0)	0.72
Single	0 (0)	0 (0)	2 (3.3)	2 (1)	0.32
Widow	3 (4.7)	6 (8)	3 (5)	12 (6)	0.41
Smoking {N (%)}					
Smoker	35 (53.8)	45 (60)	33 (55)	113 (56.5)	0.343
Non- Smoker	30 (46.2)	30 (40)	27 (45)	87 (44.5)	0.412
Comorbidities {N (%)}					
Yes	45 (69.2)	50 (66.6)	44 (73.3)	139 (69.5)	0.202
No	20 (30.7)	25 (41.6)	16 (26.6)	61 (30.5)	0.08

There was no significant difference between the three study groups in terms of BMI (P = 0.323), with the mean (SD) BMI for all patients being 41.21 kg/m2 (7.7). According to Table 1, 69.5% of the patients had comorbid conditions, primarily diabetes mellitus and hypertension, with no discernible difference.

After 2 months of treatment, all atorvastatin dose groups experienced a highly significant reduction in total cholesterol levels (P 0.05), according to Table 2.

Table 2: Effect of Atorvastatin on total serum Cholesterol level

Study Group	Variable (Total Cholesterol mg/l)		P Value
	Before Treatment (mean±SD)	**After Treatment (mean±SD)**	
Group A	230.9±22.23	185.3±33.1	0.013
Group B	242.9±31.2	230.9±34.9	0.024
Group C	278.9±38.8	230.9±37.4	0.034

After 2 months of treatment, serum TG decreased significantly (P 0.0423) in the atorvastatin 10 mg/day group and significantly (P 0.05) in the atorvastatin 20 mg/day and 40 mg/day groups, according to Table 3.

Table 3: Effect of Atorvastatin on serum Triglycerides (TG) level

Study Group	Variable (Serum Triglycerides mg/l)		P Value
	Before Treatment (mean±SD)	**After Treatment (mean±SD)**	
Group A	188.9±47.3	185.3±33.1	0.0423
Group B	194.9±51.5	230.9±34.9	0.003
Group C	205.9±58.1	230.9±37.4	0.001

After 2 months of treatment, all atorvastatin dose groups experienced a significant (P 0.05) reduction in LDL-C levels, according to Table 4.

Table 4: Effect of Atorvastatin on Low Density Lipoprotein (LDL) level

Study Group	Variable (Serum Triglycerides mg/l)		P Value
	Before Treatment (mean±SD)	**After Treatment (mean±SD)**	
Group A	148.9±27.1	115.3±23.2	0.031
Group B	154.9±31.5	119.9±34.9	0.023
Group C	187.9±34.3	122.9±37.4	0.011

There was a 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 2 months of treatment, Table 6.

Table 5: Effect of Atorvastatin on High Density Lipoprotein (HDL) level

Study Group	Variable (Serum Triglycerides mg/l)		P Value
	Before Treatment (mean±SD)	**After Treatment (mean±SD)**	
Group A	44.2±12.1	66.2±12.5	0.031
Group B	44.4±13.5	66.4±14.1	0.034
Group C	47.5±14.3	68.5±14.7	0.021

Table 6: Effect of Atorvastatin on High Density Lipoprotein (HDL) level

Study Group	Variable (Serum Triglycerides mg/l)		P Value
	Before Treatment (mean±SD)	**After Treatment (mean±SD)**	
Group A	40.2±11.1	36.2±10.5	0.021
Group B	41.4±12.5	35.4±9.1	0.014
Group C	42.5±13.3	32.59.7	0.004

DISCUSSION

In terms of morbidity, mortality, and the associated financial burden, obesity is a global public health issue. Globally, obesity was blamed for 5.0% of deaths in 2014, with a corresponding economic cost of 2.8% of gross national product (GNP). Obesity is linked to a higher risk of many chronic conditions, such as diabetes, dyslipidemia, stroke, cardiovascular disease (CVD), and some types of cancer. It is also linked to a higher risk of overall mortality and death from CVD [15]. According to a 2008 survey, the prevalence rate of obesity among adults in northern Jordan was 53.1% for women and 28.1% for men. The study also showed a rise in obesity rates in the ten years prior to the survey. In Jordan, the rise in obesity was accompanied by rises in the prevalence of diabetes, hypertension, and dyslipidemia [16]. In 2017, Jordanian adults participated in a multipurpose national household survey that lasted 4 months. The results showed that the prevalence of obesity, when measured according to age, was 60.4% for men and 75.6% for women. After adjusting for age, the odds of obesity in men and women were both two times higher in 2017 (ORs of 1.98 and 1.96, respectively) than they were in 2008 [17].

Increased triglycerides (TG) and FFA, decreased HDL-C with HDL dysfunction, normal or barely elevated LDL-C with elevated small dense LDL make up the typical dyslipidemia of obesity. Apolipoprotein B (apo) concentrations are frequently elevated as well, in part because of the hepatic overproduction of lipoproteins that contain apo B [18].

The enzyme HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol biosynthesis, is competitively inhibited by statins. The resulting decrease in hepatocyte cholesterol concentration leads to an increase in hepatic LDL receptor expression, which removes LDL and LDL

precursors from the bloodstream. Statins may reduce the production and secretion of triglyceride-rich lipoproteins and prevent the hepatic synthesis of apolipoprotein B-100 [19].

The effects of atorvastatin on LDL cholesterol over the dose range of 10 to 80 mg/d, which is the range for which this systematic review acquired the best results, were quantified in a Cochrane library systematic review to measure the effects of different atorvastatin doses on serum total cholesterol, LDL, HDL, and triglycerides in people with and without evidence of cardiovascular disease. Blood LDL cholesterol decreases by 37.1% to 51.7% within this range [20]. The purpose of this study was to evaluate how atorvastatin affected the lipid profiles of obese individuals. In the current study, the fasting plasma triglyceride concentration decreased significantly, but within previously established ranges for this drug. Studies in the HepG2 cell have shown that atorvastatin has no effect on the synthesis of triglycerides. As a result, atorvastatin's potent inhibition of cholesterol biosynthesis, which also has an impact on the secretion of apoB-containing lipoproteins, is primarily responsible for the drug's ability to lower triglycerides. As VLDL and LDL are known to compete for the same removal mechanisms, the significant decrease in the number of circulating LDL particles may also result in an increase in the removal of VLDL particles. This study demonstrated that, regardless of the dose used, atorvastatin significantly raised fasting HDL levels. This finding conflicts with those of other investigations. The HDL-C and TG levels measured after three to fourteen days of therapy in some studies looking at the short-term impact of statins on the lipid profile with stable patients showed no significant changes [21-24]. While a different study found that all atorvastatin doses significantly raised HDL-C levels. Robinson and colleagues reported a finding that was similar to ours, noting that lower baseline levels of high sensitivity C reactive protein (hs-CRP) were significantly associated with greater reductions in LDL-C, non-HDL-C, apolipoprotein-B, total cholesterol, TG, and VLDL cholesterol but not HDL-C. The decline in plasma TG levels, BMI, and alcohol consumption had an impact on the absolute increase in HDL cholesterol [25].

In summary, atorvastatin short-term therapy in obese patients decreased total cholesterol, TG, LDL, and VLDL while causing a desirable increase in HDL.

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