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ASSESSMENT OF ATORVASTATIN EFFECT ON BODY WEIGHT AND BLOOD GLUCOSE LEVELS AMONG DIABETIC AND NON-DIABETIC PATIENTS

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Abstract

Background and aims: *Atorvastatin is a member of the drug class known as statins, which used as a lipid-lowering agent. The study aim was to assess the effect of atorvastatin on body weight and blood glucose levels among diabetic and non-diabetic patients.* ***Material and Methods:*** *A 359 hyperlipidemic Jordanian patients using atorvastatin at least for 1 year were divided into two groups: diabetic (DM) and non-diabetic (NDM). The changes in lipid profile, thyroid function test, blood glucose indices as well as body weight were assessed and compared between both groups.* ***Results:*** *There was no statistical significant ($p > 0.05$) difference between means of body weight after treatment among DM (85.74 ± 3.56) and NDM (81.75 ± 1.25) groups. Descriptive statistics and mean comparisons before and after atorvastatin treatment, showed statistical significant ($p \leq 0.05$) differences in body weight and total cholesterol among NDM group and in total cholesterol and LDL-Ch among DM group. There was an increase in fasting blood glucose (FBG) and glycated hemoglobin A1c (HbA1c) and a decrease in triglycerides among both groups but the difference was not statistically ($p > 0.05$) significant.* ***Conclusions:*** *Atorvastatin may increase body weight, fasting blood glucose and HbA1c for diabetic and non-diabetic patients.*

key words: *Atorvastatin, Hyperlipidemia, Body weight, Blood glucose, Diabetes.*

Background and Aims

Atorvastatin a primary lipid-lowering agent is a member of the drug class known as statins. Statins lower cholesterol level in blood and target low-density lipoproteins (LDLs) through the inhibition of the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. Recently, through independent mechanisms statins proved to decrease about 60% of LDL paralleled with a decrease in triglycerides and a modest rise in HDL [1]. Nearly half of all men and more than half of all women aged 65 years and above, match the

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diagnostic criteria for hyperlipidemia [2]. A significant reduction in the risk of coronary artery disease (CAD) and other vascular disorders, including strokes was reported in prospective clinical trials conducted on hypercholesteremic individuals using statins for a prolonged time [3]. Based upon these findings, statins are widely prescribed in early middle-aged male and female adults for the primary and secondary prevention of CAD and stroke [4-7]. However, statins treatment is associated with side effects, the commonest of which is myopathy [8-10]. Furthermore, myopathies range from muscular disorders characterized with painless increase in serum creatinine kinase (CK) levels to a mild muscular discomfort termed myalgia, to potentially life-threatening rhabdomyolysis [8].

The potential effect of statins on blood glucose metabolism has been debatable [11,12]; some studies have reported that statins increased the risk of developing diabetes in non-diabetic patients [13,14] and negatively affected blood glucose homoeostasis in type 2 diabetic patients [12]. On the other hand, other studies reported no effect of statins on insulin sensitivity [15-17] while, others suggested a beneficial effect on glucose metabolism [18]. The mechanisms by which statins may affect blood glucose homeostasis is not clear and still under discussion [19]. Moreover, other side effects were reported to be associated with statins such as asymptomatic elevation of serum aminotransferases (alanine aminotransferase, ALT and aspartate aminotransferase, AST) [20,21], and myotoxicity [22]. In contrast, the potential negative effects of statins on body weight as well as on blood glucose levels among diabetic and non-diabetic patients are not yet well studied and have controversial results.

New side effects have been raised including increasing body weight and the risk for type 2 diabetes [23]. These side effects need further investigations to be confirmed. Therefore, the objective of this study was to assess the effect of using atorvastatin on body weight and blood glucose levels among hyperlipidemic diabetic and non-diabetic patients.

Material and Methods

Study design, selection and description of participants

The study design was a retrospective cohort study. Participants were included in the study if they are Jordanian patients aged 18 years and older, diagnosed with hyperlipidemia, using Atorvastatin 20 mg/day for at least 1 year and attending the diabetes and endocrine clinics at King Abdullah University Hospital (KAUH). On the other hand, participants were excluded from the study if their age was below 18 years, have normal blood lipid profile, using atorvastatin for a period less than one year and/or attending other clinics at KAUH. The study participants were selected by simple random sampling method from March 2016 to July 2016 and from each individual participant in the study an informed consent was obtained.

Sample size determination

The sample size allocated according to the prevalence of Jordanian patients using atorvastatin and attending the national center for diabetes, endocrinology and genetics in Jordan [24]. The sample size was calculated using the infinite population equation $n = z^2 p\ q/d^2$ [25]. Where n stands for sample size, z is the value of the 95% confidence level, q is 1-p and d is the accepted error or the precision around the population mean. Therefore, the sample size required was: $n = (1.96)^2\ (0.758)\ (0.242)\ /\ (0.05)^2 = 281.9$. To guarantee the collection of the calculated sample size and to increase the power of analysis, the number was increased to 400 patients.

Study protocol

After the hospital administration and the Institutional Research Board (IRB) committee approval, a sample of 400 patients visiting the diabetes and endocrine outpatient clinics at KAUH were selected and assessed for eligibility according to the inclusion criteria, where 41 of them were excluded. Therefore, only 359 patients were included in the study statistical analysis. Patient's names, telephone and medical record numbers were adapted from the hospital database. The laboratory results for each selected patient before and after using atorvastatin for the first year of treatment including lipid profile, thyroid function test, and glucose indices were collected from the hospital computerized information system. Meanwhile, the initial and the concurrent body weight measurements during the first year of using atorvastatin were collected from the patient medical record. In addition, a structured, reliable and valid questionnaire was completed for each selected patient through a telephone call by the research assistance, who was trained by the principal investigator. Finally, the selected patients were divided into 2 groups; diabetic (DM) and the non-diabetic (NDM). The laboratory readings as well as the changes in body weight were analyzed and compared among both groups before and after atorvastatin use.

Statistical analysis

Collected data were entered in a data sheet and analyzed using SPSS statistical package (IBM, SPSS version 20, 2011) and initially examined by performing descriptive statistics using frequency as well as means and standard error of the means to describe the categorical and numeric data, respectively. Chi-square was applied to compare frequencies of the categorical variables. The nonparametric Kolmogorov-Smirnov test was used to examine all numeric variables for normal distribution. Student t-test for independent and paired samples was used to compare means of the normally distributed numeric variables. The medians were compared when variables followed a significant skewed distribution using Mann-Whitney-U-test for the independent samples and Wilcoxon Signed Rank test was used for paired samples. In all analyses, a p-value <0.05 was considered significant.

Results

The distribution of the study sample (n = 359) according to personal information shows that 53.5% were males and 46.5% were females, 90% married, 29.2% highly educated and 51.8% had an income between 201-500 Jordanian dinar (JD). The frequency distribution of the study sample according to medical information showed that more than two thirds of the study population have chronic diseases including diabetes, hypertension, hypothyroidism and CVDs, where more than half of them have diabetes, family history of hyperlipedemia and are using atorvastatin for more than 2 years. Regarding the atorvastatin side effects, higher frequencies were reported for myopathy and increase in body weight. Meanwhile, the other side effects such as nausea, liver fibrosis, diarrhea and vomiting were reported to have lower frequencies (see Table 1).

Comparison of Atorvastatin side effects: Results from the comparison of frequencies between the diabetic and non-diabetic patients regarding the atorvastatin side effects revealed that there was a statically significant increase (P=0.001) for headache and fogy vision (P=0.003) complains among diabetic compared with the non-diabetic group, while there was a statistically significant (P=0.001) increase in diarrheal complain among the non-diabetic compared with the diabetic group (see Table 2).

Table 1. Distribution of the study sample according to medical information (N=359).

Variable	Categories	Frequency	%
Chronic diseases	Yes	314	87.5
	No	45	12.5
Diabetes	Yes	247	68.8
	No	112	31.2
Family history of hyperlipidemia	Yes	243	65.3
	No	125	34.7
Period of using atorvastatin	1 year	48	13.4
	1-2 year	50	13.9
	>2 years	261	72.7
Atorvastatin side effects			
Nausea	Yes	58	16.2
	No	301	83.8
Myopathy	Yes	248	69.0
	No	111	31.0
Liver fibrosis	Yes	9	2.5
	No	350	97.5
Diarrhea	Yes	39	10.9
	No	320	89.1
Vomiting	Yes	20	5.6
	No	339	94.4
Headache	Yes	133	37.0
	No	226	63.0
Abdominal pain	Yes	81	22.6
	No	278	77.4
Increasing body weight	Yes	166	46.2
	No	193	53.8
Fogy vision	Yes	93	26.0
	No	266	74.0

Values are presented as frequency (n) and percentages (%).

Table 2. Frequencies of the atorvastatin side effects between diabetic and non-diabetic patients.

	Diabetic (n = 247)	Non-diabetic (n=112)	*p*-value
Variable	n (%)	n (%)	(χ^2)
Nausea Yes No	 42 (17.0) 205 (83.0)	 16 (14.3) 96 (85.7)	0.677
Myopathy Yes No	 176 (71.3) 71 (28.7)	 72 (64.3) 40 (35.7)	0.115
Liver fibrosis Yes No	 8 (3.2) 239 (96.8)	 1 (0.9) 111 (99.1)	0.172
Diarrhea Yes No	 212 (85.8) 35 (14.2)	 108 (96.4) 4 (3.6)	0.001*
Vomiting Yes No	 16 (6.5) 231 (93.5)	 4 (3.6) 108 (96.4)	0.196
Headache Yes No	 105 (42.5) 142 (57.5)	 28 (25.0) 84 (75.0)	0.001*

Table 2. *Continued*.

	Diabetic (n = 247)	Non-diabetic (n=112)	*p*-value
Abdominal pain Yes No	 59 (23.9) 187 (76.1)	 22 (19.6) 90 (80.4)	 0.167
Increasing body weight Yes No	 119 (48.2) 128 (51.8)	 47 (42.0) 65 (58.0)	 0.164
Fogy vision Yes No	 75 (30.4) 172 (69.6)	 18 (16.1) 94 (83.9)	 0.003*

Values are presented as frequency (n) and percentages (%).
*Significant ($p < 0.05$) for chi-square test.

Table 3. Descriptive statistics and mean comparisons of weight, lipid profile, blood sugars and thyroid function test for diabetic and non-diabetic patients (N=359).

Variable	DM(n=247)		P-Value	None-DM (n=112)		P-Value
	Before	After		Before	After	
	Mean±S.E.M	Mean±S.E.M		Mean± S.E.M	Mean±S.E.M	
Weight (Kg)	80.55±0.79	85.74±3.56	0.14	79.75±1.42	81.75±1.25	0.03*
FBG (mmol/l)	8.72±0.58	9.06±0.34	0.31	6.94±0.81	7.36±0.86	0.48
RBG (mmol/L)	9.35±0.35	9.56±0.36	0.55	13.58±6.75	6.59±0.30	0.30
HbA1C (%)	7.84±0.21	8.10±0.21	0.16	6.62±0.25	6.73±0.30	0.71
Total-Ch (mmol/L)	5.12±0.09	4.51±0.08	0.00*	5.04±0.15	4.76±0.12	0.04*
LDL-Ch (mmol/L)	3.22±0.09	3.01±0.07	0.00*	3.20±0.16	3.22±0.11	0.07
HDL-Ch (mmol/L)	1.17±0.04	1.18±0.04	0.87	2.69±1.57	1.11±0.04	0.32
TG (mmol/L)	3.05±0.82	1.93±0.07	0.18	3.14±0.92	2.04±0.12	0.24
T3 (pmol/L)	4.17±0.10	4.08±0.09	0.33	4.19±0.28	4.12±0.19	0.77
T4 (pmol/L)	16.28±0.28	16.22±0.32	0.85	14.88±0.35	15.37±0.35	0.24
TSH (mIU/L)	2.18±0.24	2.02±0.13	0.46	2.41±0.29	2.31±0.26	0.58

Values are presented as mean ± S.E.M.
* Significant at p-value < 0.05 for paired t-test.
FBG: fasting blood glucose; RBG: random blood glucose; HbA1C, glycated hemoglobin; Ch: cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; T3: threonine; T4: thyroxine; TSH: thyroid stimulating hormone. S.E.M; standard error of the mean.

Mean comparisons before and after Atorvastatin

The mean comparisons of both study groups before and after using atorvastatin regarding body weight, lipid profile, blood sugars and thyroid function test using paired t-test analysis are shown in Table 3. Results showed that, there was a statistically significant difference (P=0.00) among the diabetic group regarding total

cholesterol, and LDL cholesterol. There were statistical increases in the means of body weight, fasting blood glucose (FBG), random blood glucose (RBG) and glycated hemoglobin (HbA1c) after atorvastatin treatment but did not reach significant level (P>0.05). Meanwhile, among the non-diabetic group there was a statically significant increase (P=0.03) in the mean of body weight after treatment and a significant decrease (P=0.04) in the mean of total blood cholesterol after treatment. Also, there was a statistical insignificant (P>0.05) increase in the means of the fasting blood glucose and HbA1c after treatment compared with the means before treatment (see Table 3).

Discussion

The aim of the study was to assess the effect of atorvastatin on blood glucose level and body weight. Our results showed an unfavorable effect of atorvastatin on glucose metabolism in diabetic and non-diabetic patients although results did not reach statistical significant level, which could be attributed to the small sample size. Our results come in concordance with other studies like Moutzouri et al. [26] which compared the effects of statins like simvastatin and found significant increase in HOMA-IR and fasting insulin levels with no change in FBG, HbA1c and HOMA-B levels compared with baseline. Cederberg et al. [27] proved that statins increased the risk of type 2 diabetes by 46% due to the decrease in insulin sensitivity and secretion. Moreover, Castro et al. [28] found a positive association between statin use and increased incidence of diabetes in both normoglycemic and impaired fasting glucose (IFG) patients. On the other hand, Guclu et al. [29] noted a statistical significant decrease in HOMA, postprandial and fasting glucose levels and HbA1c values after treating metabolic syndrome patients with pravastatin. Conversely, other statins including atorvastatin, rosuvastatin, and simvastatin all promote significant increase in new onset of diabetes [30].

In our study, a significant increase in body weight of non-diabetic atorvastatin treated patients was noted. However, a nonsignificant weight increment in diabetic patients was recorded. The weight gain with statin use is not well explained, some studies showed that statins increase body and liver fat accumulation in obese Zucker rats [31]. Another study by Ong et al. [32], reported a significant increase in body weight after one year of atorvastatin randomization, where the increase in body weight was greater in patients with new onset diabetes mellitus (NODM) than those without (NODM). Even though in general, the loss of fat free mass (FFM) is associated with aging, the loss of FFM and the increase of fat mass was more pronounced in statin treated patients than in non-statin users [33].

Nonetheless, it is widely accepted that statins significantly decrease the incidence of cardiovascular complications, and the great benefit of statins outweigh the smaller risk of glucose impairment or weight gain in high risk populations [34,35]. Our results also showed a higher risk of side effects in diabetic patients using statins compared to non- diabetics which comes in concordance with other studies [8-10].

Finally, the study had limitations including the retrospective design and the small sample size. Therefore, larger sample size population and double -blinded placebo controlled clinical trials would help confirm these associations.

Conclusions

Atorvastatin drug was effective in lowering total blood cholesterol levels, LDL and triglycerides level, whereas, it increased the blood level of the HDL cholesterol. Also, atorvastatin may increase body weight, fasting blood glucose levels and HbA1c for diabetic and

non-diabetic patients, which will increase the risk of type 2 diabetes mellitus among the non-diabetics and increase the adverse effects of un-controlled blood sugar among diabetic patients. Diabetic patients suffer from atorvastatin side effects of diarrhea, headache, fogy vision, myopathy and increase in body weight more than the non-diabetic patients do. Therefore, routine medical follow-up, monitoring and evaluation of body weight and blood glucose levels is highly recommended for diabetic and non-diabetic patients.

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