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Investigating the effect of atorvastatin drug on HbA1c in patients with myocardial infarction hospitalized in Farshchian Hospital, Hamadan province, Iran, in 2014-2015 (a before-after study)

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ABSTRACT

Use of statins reduces the risk of cardiovascular diseases, however, in some studies, contradicting results about statins especially atorvastatin with the risk of diabetes have been reported. The purpose of the present study, was to investigate the effect of atorvastatin drug on HbA1c in patients with myocardial infarction hospitalized in Farshchian Hospital, Hamadan. 60 patients hospitalized in CCU, who were diagnosed with one type of infarction were included in this clinical trial performed as a before-after study. Demographic data were collected using a questionnaire. Before the study and 6 months after the start of the study, the parameters of lipid profile, HbA1c and GFR were measured. Atorvastatin with a dose of 80mg was given to the patients from the beginning of the study for 6 months. The results were analyzed using SPSS. The average age of the male and female patients was 63.83 and 61.11, respectively, which had an insignificant difference. 42 patients (70%) were male and the rest of them were female. Lipid profile results at the end of the study showed improved averages for the parameters, all of which were statistically significant compared to their values at the start of the study. The mean HbA1c increased from 6.19 to 6.43 (P=0.001), the mean fasting blood sugar increased from 103.66 to 110.51 (P=0.001), and the average glomerular filtration rate (GFR) decreased from 69.84 from the start of the study to 67.43 which was statistically significant (P=0.002). Systolic and diastolic blood pressure at the end of the study decreased compared to the start of the study where in systolic blood pressure, this decrease was significant (p=0.003). Based on the results of this study, although the use of atorvastatin reduces lipids, it may create the risk of hyperglycemia in these patients. However, a certain conclusion requires further studies.

Keywords: statin, HbA1c, type 2 diabetes

INTRODUCTION

Atorvastatin is from the category of statin drugs and an inhibitor of HMG-CoA enzyme of Hepatic Reductase which through the inhibition of cholesterol synthesis in the liver, significantly decreases the blood LDL level and prevents the progression of its complications, especially cardiovascular problems (1). Atorvastatin is used for people with hyperlipidemia or any type of atherosclerotic cardiovascular diseases because in addition to its lowering effect on blood lipids, it has good digestive tolerance and is rapidly absorbed from the digestive tract (2). This drug is used for primary prevention of heart attack and stroke in patients with risk factors such as history of hypertension, smoking, high LDL and low HDL and positive family history of coronary artery disease and also for secondary prevention in patients with myocardial infarction and individuals with unstable angina (3). Studies have shown that on average, atorvastatin decreases the risk of ischemic heart disease and heart attack by 60% and 17%, respectively (4). However, based on studies performed in the past, it improved prognosis in ischemic heart disease patients and increased the lifetime of this group of patients and has been used as a main drug for this category of patients (5). Over the past few years, new effects of statins not related to decreased cholesterol have been identified. The effect of atorvastatin drug on decreased serum

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lipid profile particularly LDL in several studies has been clearly confirmed, including: 1) in patients with tri glyceride of higher than 250, it decreases its level by 25-60% on average. 2) If the HDL level is low, it increases its level by 20-30% (4). Of the side effects of this drug discovered in clinical trials, the following ones can be mentioned: 1) mild increase in serum transaminases 2) increased creatine kinase (skeletal muscle) seen in 10% of the patients and in a few of the patients, severe muscle pain and even rhabdomyolysis was created (6).

Diabetes is one of the most common chronic diseases caused by metabolism disorders that disrupts blood sugar metabolism and eventually leads to increased hyperglycemia (7). One of the specialized and accurate experiments to diagnose diabetes is the measurement of the level of HbA1c which is the product of a process called glycolysis which is created in the hemoglobin of a person's red blood cells. This marker shows the average sugar in the blood of a person over the past 3 months (8). The normal level of HbA2c in individuals with normal blood sugar (FPG<100) is less than 5.6%, whereas this value in people with diabetes is more than 5.6% (9). This test is very specialized and sensitive for plasma blood glucose measurement, it has its limitations such as: in individuals who recently lost a lot of blood or have a type of hemoglobinopathies such as sickle cell anemia or hemolytic anemia, its measurement is worthless (10).

A great meta-analysis was performed in 2012 to determine the effect of statins on the level of blood sugar in patients with diabetes. In this meta-analysis, the results of 26 studies were evaluated in terms of the amount of HbA1c. In these studies, all the participating individuals had type 2 diabetes and had already been undergoing treatment with statins. The results of these studies indicated a lack of a significant effect on the HbA1c of these individuals (11). A prospective study was performed in 2016 by Lin et al. on patients with Acute Coronary Syndrome who used statin, to investigate the emergence of diabetes in Taiwan. 9043 individuals who used statins were compared with 9043 individuals who did not use statins. Individuals who recently used statins, showed a significant 27% emergence of diabetes. Based on the results of this study, a relationship between the emergence of diabetes and use of statin in cardiovascular patients is seen, but due to the preventive effect of statins for prevention of morbidity and mortality, use of statins is still advised for these patients (12).

The results of some other studies show the effect of using statin, on increasing the risk of diabetes (14,13) and increased HbA1c in patients with and without diabetes (15,16). In another study, use of statin in patients with type 1 diabetes was accompanied by increased HbA1c in these patients. Based on the results of this study, given the effects of statin on cardiovascular diseases, use of these drugs should not be avoided for patients with type 1 diabetes, in these patients, insulin dosage must be revised (17).

Few studies have investigated the effect of changing the dose of atorvastatin and its negative effects on the amount of HbA1c, therefore, in this study, it was tried to investigate the effect of atorvastatin on HbA1c which is a specialized and sensitive indicator for identification of patients with diabetes.

MATERIALS AND METHODS

Given the absence of any similar studies in this field and impossibility to use the sample size formula, all patients suffering from myocardial infarction hospitalized in CCU, were included into the study for two months since the beginning of the research via the census method. Study exclusion criteria included: 1) history of diabetes or any type of diabetes, 2) history of atorvastatin use and 3) censoring of the study samples during the follow-up period. All the patients at the beginning of the study and before receiving atorvastatin, were at aseptic state and had not eaten or drunken anything for 8 hours, and 5cc of blood was taken from them for HbA1c, HDL, TG, LDL, and GFR tests which were performed under standard conditions. Atorvastatin drug with a dose of 80mg was given to the patients from the beginning of the study for 6 months. After this period, the values of said factors were re-measured and evaluated. The data of this study was analyzed using the SPSS software and appropriate statistical tests at the significance level of 0.05.

RESULTS

In this clinical trial performed as a before-after study, 60 patients with myocardial infarction who met the study inclusion criteria were included into the study. The significance level was considered as 0.05.

The majority of the study participants were male such that 42 (70%) of the participants were male and 18 (30%) were female. The average age of the females was 61.11 whereas the average age of the males was 63.83, and this difference was not statistically significant (**Table 1** and **2**). Due to the high average age of the patients in the study, they were categorized into the two categories of younger than or equal to 60, and older than 60 for hypotheses testing.

Table 1: *Frequency distribution of the participants based on gender*

Gender	Frequency	Percentage
Male	42	70
Female	18	30
Total	60	100

Table 2: *Comparing the average age of the males and females participating in the study*

Gender	Average age	p-value (Mann-Whitney)
Male	63.83	0.392
Female	61.11	

Table 3: *Comparing the glomerular filtration rate (GFR) and lipid profile before and after intervention*

Variable		Before intervention	After intervention	p-value (chi2)
GFR	60mL/min ≥	21 individuals (35.0%)	23 individuals (38.3%)	0.705
	60mL/min <	39 individuals (65.0%)	37 individuals (61.7%)	
LDL	100 ≥	21 individuals (35.0%)	28 individuals (46.7%)	0.194
	100 <	39 individuals (65%)	32 individuals (53.3%)	
HDL	50 ≥	36 individuals (60.0%)	33 individuals (55.0%)	0.595
	50 <	24 individuals (40.0%)	27 individuals (45.0%)	
TG	150 ≥	34 individuals (56.7%)	33 individuals (55.0%)	0.854
	150 <	26 individuals (43.3%)	27 individuals (45.0%)	
FBS	100 ≥	32 individuals (53.3%)	22 individuals (36.7%)	0.067
	100 <	28 individuals (46.7%)	38 individuals (63.3%)	

Table 4: *Comparing the variables before and after the study in the study participants*

Variable	Mean before intervention	Mean after intervention	p-value
HbA1c	6.19	6.43	0.001
LDL	122.03	117	0.001
HDL	48.26	49.33	0.001
TG	172.46	163.08	0.001
GFR	69.43	67.43	0.002
FBS	103.66	110.51	0.001
Systolic pressure	126.83	119.33	0.003
Diastolic pressure	79.16	76.33	0.081

Table 5: *Comparing the mean HbA1c in the study participants based on*

Variable		Mean before intervention	Mean after intervention	p-value
Gender	Male	6.18	6.38	0.001
	Female	6.20	6.55	0.004
Age	60 ≤	6.06	6.29	0.001
	60 <	9.29	6.55	0.002
GFR	60 mL/min≤	6.43	6.83	0.001
	60 mL/min<	6.05	6.20	0.098
LDL	100 ≥	6.31	6.38	0.623
	100 <	6.12	6.46	0.001
HDL	50 >	6.32	6.53	0.027
	50 <	6.0	6.28	0.001

Comparison of the amount of glomerular filtration rate (GFR) and serum lipid profiles before and after intervention, does not show any significant difference (**Table 3**). Comparison of the variables of HbA1c, LDL, HDL, TG, GFR, FBS, systolic pressure and diastolic blood pressure in the participants before and after the study showed that in all the items except for the mean diastolic blood pressure, the difference was statistically significant (**Table 4**).

Comparison of the mean HbA1c in the participants was performed based on the variables of gender, age, GFR, LDL and HDL, where in all the items except for LDL≤100, HDL≤50 and GFR>60mL/min, the difference before and after the study was significant (**Table 5**).

Figure 1 shows the difference between hemoglobin A1c at the beginning and end of the study.

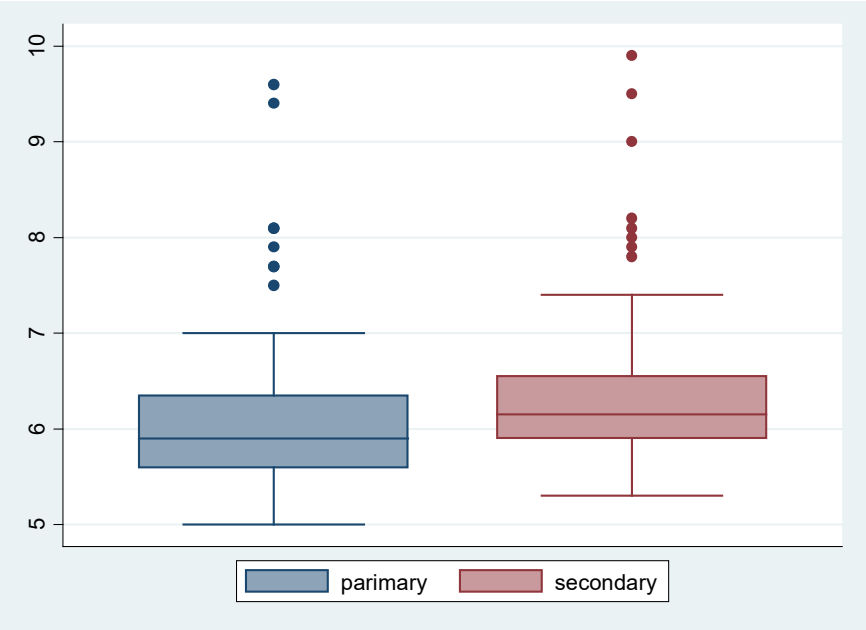

Figure 1: *Rod box diagram of A1c hemoglobin at the beginning and end of the study*

Table 6: *Comparing lipid profile in the study participants based on age groups before and after the study*

Variable		Mean in ages equal to or younger than 60	Mean in ages older than 60	P value
LDL	Before intervention	115.71	112.17	0.012
	After intervention	127.56	122.28	0.001
HDL	Before intervention	49.21	50.46	0.001
	After intervention	47.43	48.34	0.036
TG	Before intervention	172.17	166.25	0.071
	After intervention	172.71	160.31	0.001

Also, comparison of lipid profile in the participants was performed before and after intervention in the two age groups of older and younger than 60. This comparison shows that except for the variable of LDL before intervention, HDL after intervention, also the TG variable before intervention, in the rest of the variables, the difference between the two age groups was statistically significant (**Table 6**).

DISCUSSION

In addition to decreasing cholesterol synthesis in the liver, statins prevent or stabilize atherosclerotic, decrease the accumulation of plaques, improve vascular endothelial function, decrease vascular inflammation and decrease the accumulation of plaques in the body (18, 19). Early consumption of statins in patients suffering from Acute Coronary Syndrome can despite the high level of blood cholesterol, have suitable effects on decreasing mortality in these patients and according to some clinical trials, early use of these compounds in patients with acute myocardial infarction even with high blood fat is advised (20). Although the results of some past studies indicate an increase in blood sugar among people consuming statins particularly atorvastatin, but few statins have focused on the effect of statins on HbA1c (12, 18, 21, 20).

Our study results showed that in individuals who started consuming atorvastatin for the first time or did not have a history of using it over the past 6 months, after 6 months of using it for a daily 80mg, this drug increases the mean HbA1c from 6.19% at the beginning of the study to 6.43% at the end of the study, which is a statistically significant increase. In a study performed by Nobuhiro et al. in 2016 in Japan, it was discovered that in people with a history of diabetes, use of statin caused a significant HbA1c increase from 7.18 to 7.57 which matches the results of our study. Also the authors of this paper concluded that this increase was seen in people without a history of diabetes like in our study (15). The results of a meta-analysis performed by Erqou et al. showed an increase in HbA1c in people who used statin, such that there was an increase of 1.3mmol/mol in the study group compared to the control individuals which matches the results of our study (21). The results of a cross-sectional study in 2016 performed by Jensen, it was discovered that the use of statin in patients with type 1 diabetes leads to the increase of HbA1c in these patients (17). The results of a

parallel-group, phase IIIb, multi-centre study showed that the use of statins is accompanied by the increase of HbA1c in these patients. In this study, the two drugs of atorvastatin and rosuvastatin were compared where both drugs caused an increase in HbA1c but the incremental effect of atorvastatin on HbA1c was higher which seems that statins have different effects on HbA1c, and this difference can be compared among patients and the best drug can be selected (16).

The results of past studies show an effect related to the dose for statins and increase of hyperglycemia in high doses of statin and it seems that in patients who get a high level of HbA1c, if it is possible, especially for patients with diabetes, selection of an appropriate dosage of medicine reduces the complications of hyperglycemia (22). The results of this study showed that the use of atorvastatin leads to the increase in fasting blood sugar levels and an increased risk of hyperglycemia in these patients. Such that the average fasting blood sugar (FBS) increased from 103.66mg/dL to 110.51mg/dL which was statistically significant. As was expected, use of statins led to the decrease of LDL and TG averages in these patients such that the average of LDLMG/dl decreased from 122.03 to 117Mg/dl and the average of tri glyceride decreased from 172.46Mg/dl to 163.08Mg/dl both of which were statistically significant. The average HDL also increased from 172.46Mg/dl to 163.08Mg/dl which was significant. Of the unexpected results of our study, was the decreased renal function at the end of the study where the average of GFR decreased from 69.84ml/min to 67.43ml/min which may be due to the clinical conditions of our study participants. In a study by Kakuda et al. in 2015, increase in HDL after the use of statin, improved renal function (12).

At the end, although it is necessary to control hyperlipidemia and keep the fat level at an optimal level in patients to prevent cardiovascular complications, it is necessary that these individuals be cared for in terms of high blood sugar and hyperglycemia so when necessary, they would have an appropriate treatment for control of hyperglycemia's side-effects.

CONCLUSION

Based on the results of this study, although the use of atorvastatin leads to decreased lipids and probably a decreased risk of cardiovascular diseases in these patients, but it can still cause increased risk of hyperglycemia, increased HbA1C and emergence of diabetes in these patients. However, confirmation of the results of this study requires further studies in the future.

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