

Comparing the Effects of Atorvastatin on LDL Reduction through Systematic Review Method and Meta-Analysis

Samiramiss Qavam¹, Masoumeh Shohani², Firoz Balavandi¹, Ramak Qavam³ & Hamed Tavan²

¹ Department of Cardiology, Hospital of Shahid Mostafa Khomeini, Ilam University of Medical Sciences, Ilam, Iran

² Nurse, Faculty of Nursing and Midwifery, Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran

³ Colorectal Research Center, GI fellow, Rasoul-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

Correspondence: Hamed Tavan, Iran, Ilam University of Medical sciences, Faculty of Nursing and Midwifery, PO Box: 69391-77143, Ilam, Iran. Tel: 98-841-222-7123; Fax: 98-841-222-7134. E-mail: hamedtavan@gmail.com

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Abstract

Background and Goal: LDL is one of the important risk factors that cause cardiovascular diseases. Improving one's lifestyle accompanied by taking medicine can be effective in reducing the amount of LDL. This study aims at comparing the effects of Atorvastatin on reducing LDL using systematic review method and meta-analysis.

Materials and Methods: In this systematic review, Pub Med, Scopus, Elsevier and Google Scholar search engine were applied to do a search within the time span of 2003-2014 using standard key words. Articles which met the entrance criteria were studied. Random effects model was used to integrate the results through meta-analysis. Data were analyzed using Stata software (version 11.1).

Findings: In a systematic review, 11 articles were passed through the process of meta-analysis with a sample size of 3662 individuals and a mean of 333 subjects per study. The rate of LDL reduction was 33.32 milligrams per Deciliter by Atorvastatin. The meta-regression graph based on age showed that in the studies where the age of the sample has been younger, the amount of LDL has been higher and in studies with older sample age, the LDL rate has been lower. The meta-regression graph to BMI showed that people with higher BMI, showed more reduction in LDL and individuals with lower BMI, indicated less LDL reduction.

Conclusion: According to the results of the study, LDL reduction takes place better and more quickly in the elderly and fat individuals. Atorvastatin was more effective in reducing the rate of LDL.

Keywords: Atorvastatin, LDL, meta-analysis, systematic review

1. Introduction

Among the cardiovascular diseases, Coronary Artery Disease (CAD) is the major cause of death or disability. Medicinal methods, interventional procedures and surgery are used to treat CAD (Di Angelantonio, 2010; Genser, 2008). One of the methods used in recent years to reduce myocardial necrosis while carrying out PCI, has been the use of Statin medicines especially Atorvastatin and Rosuvastatin (Higgins, 2011; Begg & Mazumdar, 1994). Some trial studies showed that using Atorvastatin reduces the rate of myocardial infarction, MI around non-emergency PCI operations (Egger et al., 1997; Anagnostis et al., 2011). In addition, a few studies showed that using a high dose of Atorvastatin such as a single 80 mg dose or Rosuvastatin such as a single 40 mg dose one day before PCI would reduce the rate of infarction around PCI (Ferdinand et al., 2006; Milionis et al., 2006).

Other studies showed that the rate of LDL is related to the risk of myocardial infarction atherosclerosis and if we can reduce the amount of LDL, we would be able to decrease the risk posed by those diseases. Healthy diet, doing exercise and mild physical activities are some of the ways that can prevent LDL increase (Brunetti, 2007; Stalenhoef, 2005). Studies indicate that Atorvastatin and Rosuvastatin reduce LDL but there are not any meta-analytical studies that can tell us exactly what dose of Atorvastatin or Rosuvastatin would reduce how many milligrams of the initial LDL and what dose of the medicines (Atorvastatin 40 mg or 80 mg, Rosuvastatin 40 mg or

20 mg) would reduce what amount of body fat. Since numerous studies have been conducted about the effects of Atorvastatin and Rosuvastatin on LDL reduction and in order to validate the results of those studies, it seems necessary to carry out a meta-analysis so that precise and valid doses are provided for planners and researchers in this field. The aim of this study is to determine and compare the amounts of LDL reduction caused by Atorvastatin and specify those amounts according to geographical region, patients' age, year of study, sex and risk factors through meta-analysis.

2. Materials and Methods

This study is a systematic review which adopts a meta-analysis method. The data for this study are extracted from articles published in PubMed, Scopus, Elsevier and Google Scholar. Valid key words such as “meta-analysis”, “Rosuvastatin”, “Atorvastatin” and “reduction of LDL” and their possible combinations were searched using AND and OR operators.

2.1 Selection of Studies and Data Mining

First, the researchers collected all articles related to the effect of Atorvastatin on LDL reduction and after that prepared a list of article abstracts. So, all papers in whose titles the phrases “effect of Atorvastatin and LDL reduction” appeared were put on the list and other studies which discussed Atherosclerosis treatment through surgery and risk factors that increase LDL were set aside. In the next step, a checklist of the essential data for the study (researcher's name, article title, year, place, number of subjects in the sample, number of male subjects, number of female subjects, effects of Atorvastatin on LDL reduction among men (before treatment and after treatment), effects of Atorvastatin on LDL reduction among women (before treatment and after treatment), amount of LDL reduction based on time, amount of LDL reduction based on sample size, place of conducting the study shown by a code, age group, LDL risk factors and their subcategories which had been initially assessed were used for final evaluation. Finally, the researchers examined the eventual checklist and the articles related to the study entered the meta-analysis phase. In the primary search, 60 papers were made accessible using standard key words and 30 of them which had relevant topics were put on the list of article abstracts. Eventually, the articles were qualitatively assessed using a checklist of parameters including sample size, time of conducting research, effect of Atorvastatin on LDL reduction (before and after treatment), in male and female subjects. Papers which studied the rate of LDL reduction (before and after treatment), due to Atorvastatin use went through final confirmation. In the end, nine appropriate articles entered the process of meta-analysis. The whole texts of the articles were reviewed during analysis.

2.2 Statistical Analyses

Since the effect of Atorvastatin on the rate of LDL (before treatment and after treatment) and sample size had been extracted from each article, binomial distribution was used to calculate the variance of each study. To blend different rates of LDL reduction, weighted average was used. A weight was given to each study proportionate to its inverse variance. Due to great differences in LDL reductions in different studies (i.e. heterogeneity of the studies) and significance of the heterogeneity index (I^2), random effects model was used in the meta-analysis. The rate of heterogeneity in this study was 98.141% which puts it in the category of studies with severe heterogeneity (Low heterogeneity is when I^2 index is smaller than 25%, it is medium when the index is between 25% and 75% and high when the index is above 75%).

Meta-regression analysis was used to compare the effects of Atorvastatin on LDL reduction taking into account the year in which the study was conducted and investigating the reason for which the results became heterogeneous. The effects of Atorvastatin on LDL reduction among male and female subjects (before treatment and after that) were studied considering LDL reduction based on time, sample size, age group and year of the study through the analysis of subcategories. Data were analyzed using STATA software (version 11.1).

3. Findings

In a systematic review of 60 articles, abstracts of 30 papers were selected after investigating the topics and different aspects to be studied were extracted from the abstract and put on the checklists. After the final analysis, 11 papers were checked and passed through the checklist and the researcher gained access to the full texts of the articles (Figure 1: the study's flowchart).

The eventual investigations were completed between 2003 and 2014. The total sample size was 3662 people with a mean of 333 individuals in each study. Globally, six studies were conducted in Asia (54.54%) in the countries of South Korea, Japan and China, three studies (27.27%) were carried out in Europe in the countries of Finland, Greece and Italy, one study was performed in America (9.09%) and one study was conducted in Africa (9.09%).

Sampling method in all these studies was in the form of listing the researches that met the criteria of entrance. These criteria included reporting the rate of LDL (Milligrams in Deciliter) before and after therapy and estimating the effects of Atorvastatin on LDL reduction. The least amount of LDL reduction by Atorvastatin was reported in Keith (2006) in Africa which was 31.8 milligrams per deciliter and the highest amount was reported in Anagnostis (2011) in Greece which showed 82 milligrams per deciliter reduction in LDL. The information about the articles investigating the effect of Atorvastatin on the rate of LDL reduction is shown in Table 1.

Due to heterogeneity of the studies (I^2 index = 98.48%), confidence intervals for each study and for all studies based on the random effects model are shown in graph 1 A) Forest plot for the effect of Atorvastatin on LDL reduction before treatment .

Graph 2 A) is the forest plot for the effect of Atorvastatin on LDL reduction before treatment. The initial LDL reduction rate using Atorvastatin was 42.098 milligrams per deciliter with the significance level of $P=0.000$ and I^2 index was 98.141%. LDL reduction rate was 33.23 milligrams per deciliter with the significance level of $P=0.000$ and I^2 index of 98.489%. High I^2 index shows that the results of the studies are drastically different from one another and low I^2 indicates that the results are significantly similar.

Meta-regression graph of the studies based on age, shows that in the studies where the sample's age were young, the rate of LDL was high and in the studies where the sample's age was older, LDL had a lower amount (graph 3).

Meta-regression graph of the studies based on BMI shows that individuals who had higher BMIs, their LDL was reduced more and people who had smaller BMIs, showed less LDL reduction. It means that the higher the weight, the more LDL would be reduced through Atorvastatin consumption (graph 4).

Publication bias obtained through the results is shown in graph 5 and indicates that in this type of studies, bias has not had any effect. It is shown in the form of symmetry in a funnel-shaped graph. The sizes of circles show the weights of the studies (Greater circles have more subjects in their samples and the smaller circles have less subjects).

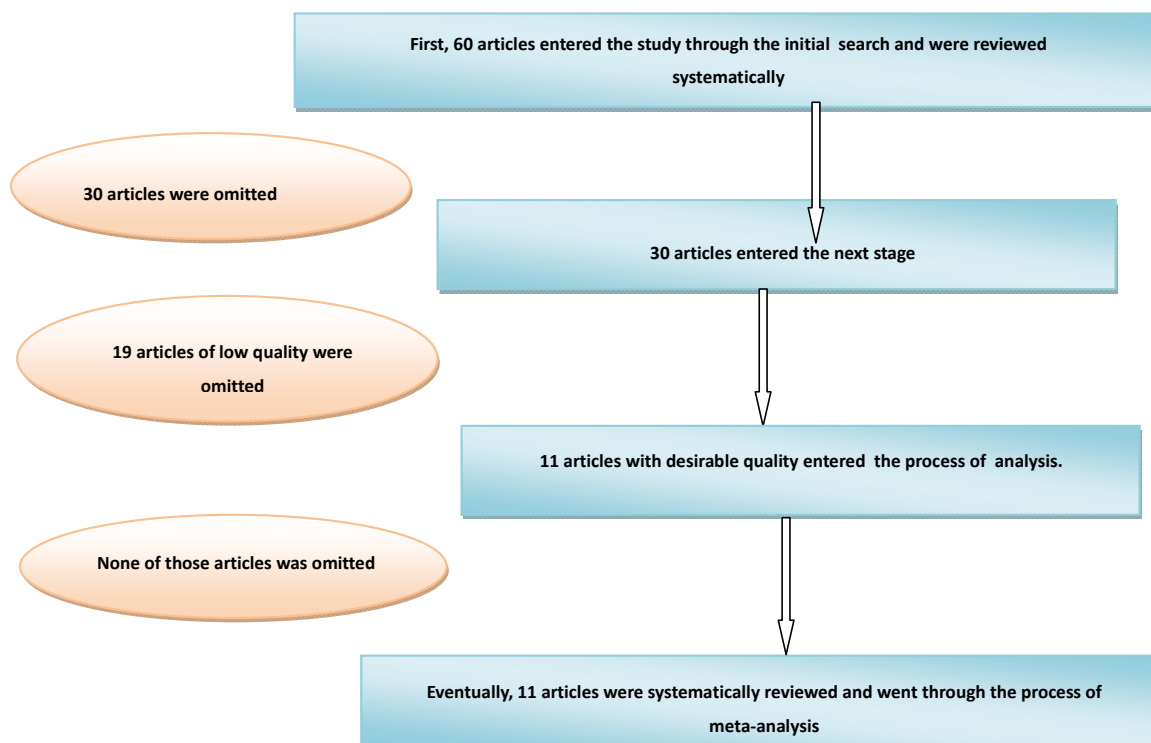
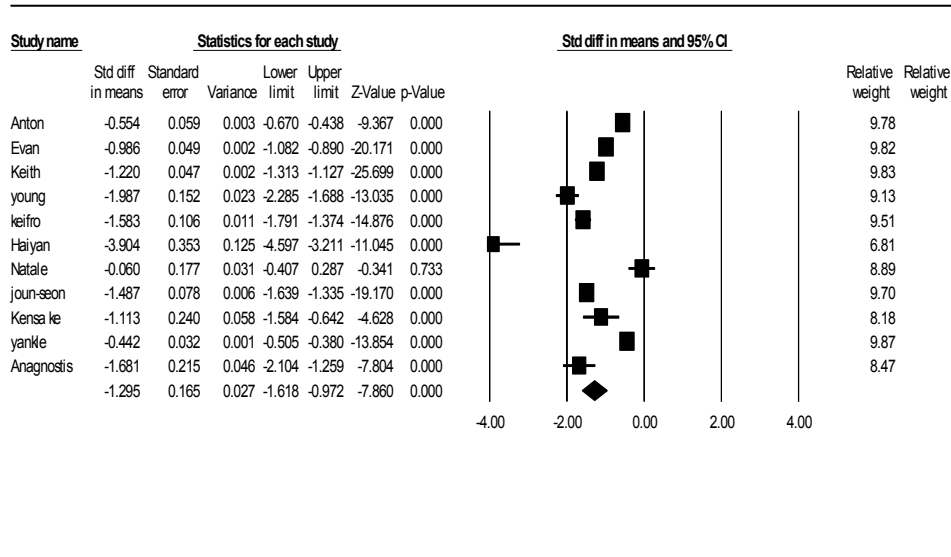


Figure 1. Flowchart of the stages that studies go through to enter the processes of systematic review and meta-analysis

Table 1. Characteristics of the articles under investigation related to the effect of Atorvastatin on LDL reduction in Mg/dl

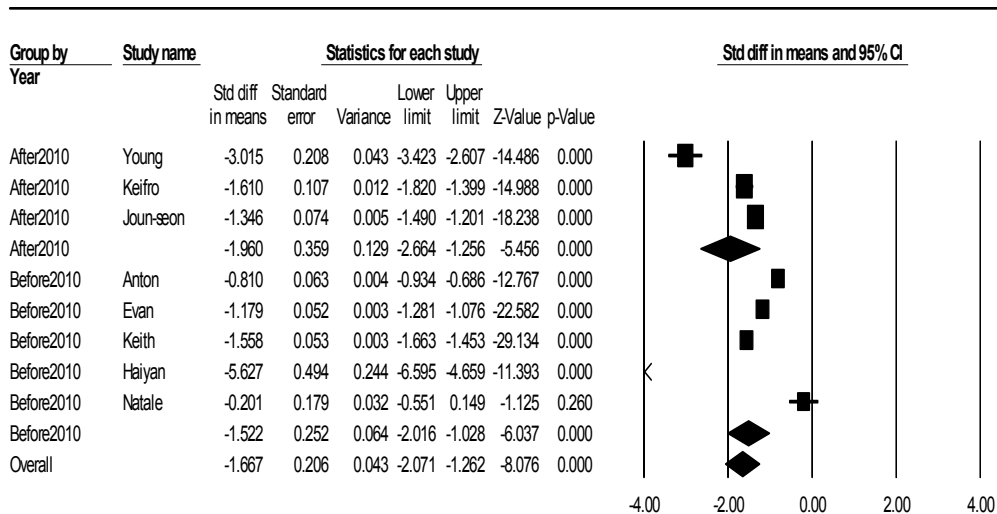
Change LDL(Mg/dl)	LDL(after treatment)	LDL(initial)	Male(N)	Female(N)	Numbers	Year	City	Aoutor
42.5 Mg/dl	218.5	261	100	65	165	2005	Fanland	Anton 11
50.4 Mg/dl	237.6	288	80	107	187	2003	USA	Evan 12
31.8 Mg/dl	157.3	189.1	133	250	383	2006	Africa	Keith13
47 Mg/dl	70	117	63	17	80	2011	South Korea	Young 14
69 Mg/dl	93	162	34	65	99	2011	Japan	Keifro 15
51.78 Mg/dl	91.48	142.26	34	20	54	2009	China	Haiyan 16
3.9 Mg/dl	95.2	99.1	11	5	16	2007	Italy	17 Natale
65.48 Mg/dl	98.37	163.85	67	111	178	2010	South Korea	joun-seon 18
54 Mg/dl	75	129	21	7	28	2012	Japan	Kensa ke 19
-	-	149	618	187	805	2014	China	20yankle
82 Mg/dl	110	192	10	42	52	2011	Greece	Anagnostis 21

Numbers indicate the reference numbers in the text.

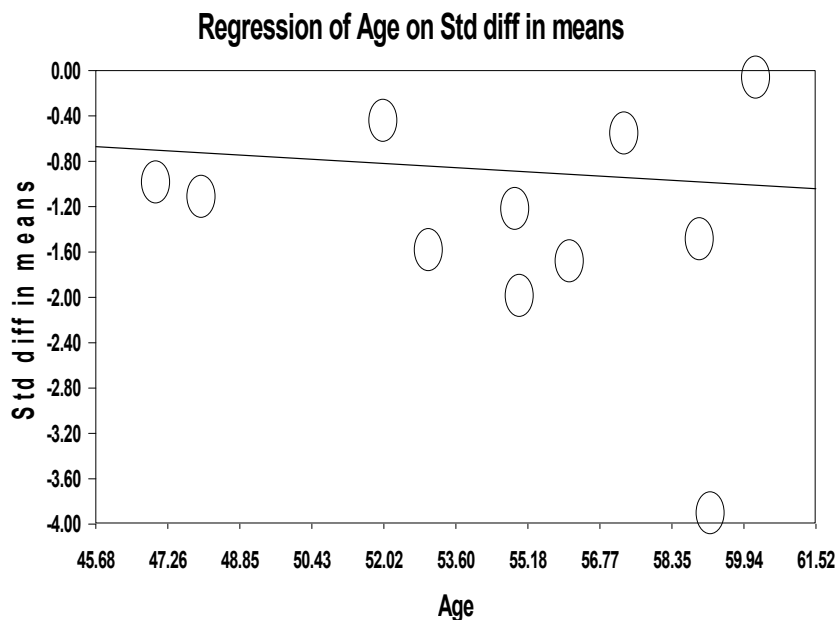


Forest plot for the effect of Atorvastatin on LDL reduction before treatment with the confidence interval of 95%

Graph 1. Effect of Atorvastatin on LDL reduction before treatment with the confidence interval of 95% generally and separately for all studies according to random effects model, segments show the confidence interval for amount of LDL reduction in each study. The middle point in each segment is an estimation of the amount of LDL reduction in each study. The diamond shows the confidence interval for the amount of LDL reduction for all the studies

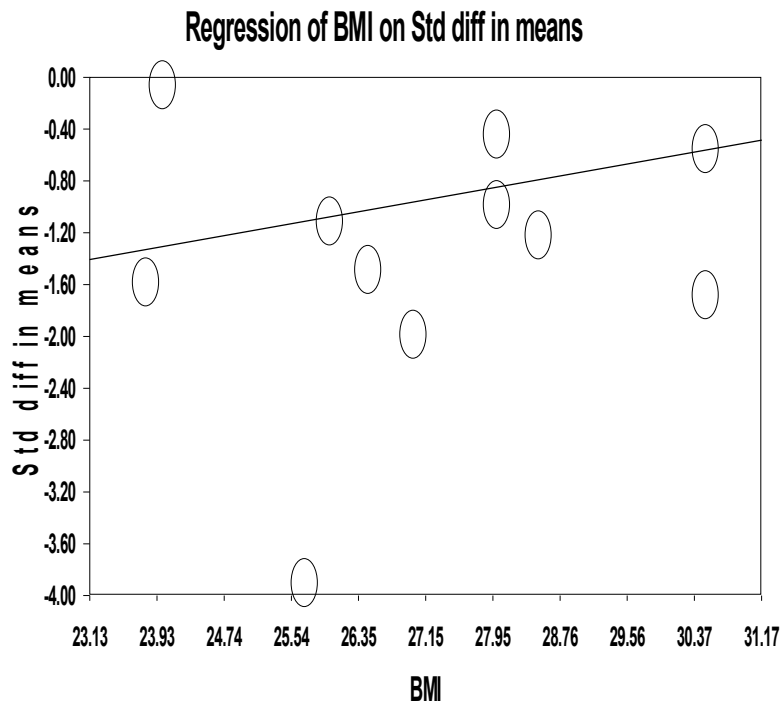


Forest plot for the effect of Atrovastatin on LDL reduction after treatment with the confidence interval of 95% Graph 2. The amount of Atrovastatin effect on LDL reduction after treatment with the confidence interval of 95% generally and separately for all studies based on the random effects model, segments show the confidence interval for amount of LDL reduction in each study. The middle point in each segment is an estimation of the amount of LDL reduction in each study. The diamond shows the confidence interval for the amount of LDL reduction for all the studies



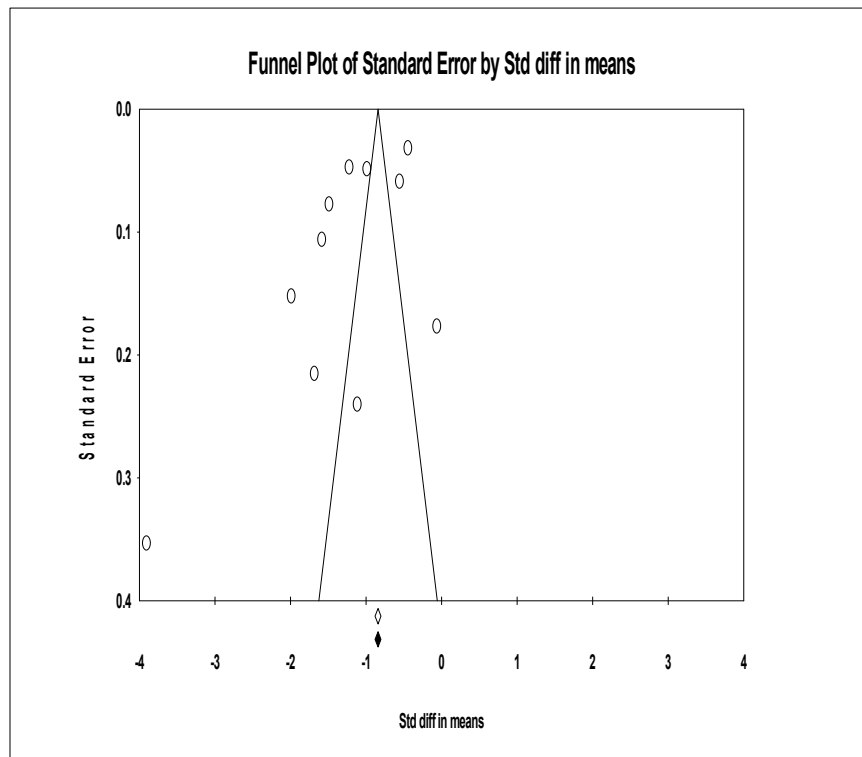
Graph 3. Meta-regression of the studies according to age:

This figure shows the relationship between age and the amount of LDL through Atorvastatin treatment. In the studies where the subjects are younger, the amount of LDL is higher and in those where the subjects are older, the amount of LDL is lower.



Graph 4. Meta-regression of the studies according to BMI and LDL reduction relationship through the use of Atorvastatin

This figure shows that in the individuals with higher BMI, LDL reduction is more and in subjects with lower BMI, LDL reduction is lower.



Graph 5. Publication bias of the articles according to Atorvastatin effect on LDL reduction

Publication bias obtained through the results is shown in figure 5 and indicates that in this type of studies, bias has not had any effect and it is shown in the form of symmetry in a funnel-shaped graph. The sizes of the circles show the weights of the studies (greater circles have a higher number of samples and smaller ones have a lower number of samples).

4. Discussion

11 studies were conducted between 2003 and 2014. The total sample size was 3662 subjects with an average of 333 individuals in each study. The distribution of the studies in the world shows that six studies (54.54%) were conducted in the Asian continent in the countries of South Korea, Japan and China, three studies (27.27%) were performed in the European continent in the countries of Finland, Greece and Italy, one study (9.09%) was carried out in the American continent and one (9.09%) was conducted in the African continent.

According to the results of the study, the initial LDL reduction through Atorvastatin was 42.098 milligrams per Deciliter and the amount of LDL reduction after treatment by Atorvastatin was 33.23 milligrams per deciliter (Stalenhoef et al, 2005; Stein et al., 2003; Ferdinand et al., 2006; Hong et al., 2011; Saku et al., 2011; Qu et al., 2009; Brunetti et al., 2007).

The results of this study showed that the relationship between age and LDL reduction through Atorvastatin is significant. In studies where the ages of the people participating in the study was younger, the rate of LDL was high and in the studies where the ages of the people in the sample was older, the rate of LDL was lower. It can be said that LDL decreases more and faster in older people than younger ones and it can be controlled better. These results are consistent with the results of other studies (Park et al., 2010, Toyama et al., 2012, Liu et al., 2014 and Anagnostis et al., 2014).

According to the results of the study, the relationships between BMI and LDL reduction through Atorvastatin are significant. Thus, in subjects with higher BMI, LDL reduction is more and in subjects with lower BMI, LDL reduction is less. It can be concluded that Atorvastatin can reduce LDL faster in fat people compared to thin individuals. Other studies show similar results (Stalenhoef et al., 2005, Hong et al., 2011 and Park et al., 2010).

The results also show that the lowest amount of LDL reduction using Atorvastatin is 31.8 milligrams per deciliter (Ferdinand et al., 2006) and the highest rate of reduction by Atorvastatin is 82 milligrams per deciliter (Anagnostis et al., 2014). The average reduction by Atorvastatin is 33.33 milligrams per deciliter and this rate is consistent with the result of Keith's study and inconsistent with that of Anagnostis. Different statistical populations and different times at which the studies were conducted can be the reasons for this inconsistency.

Differences in the statistical population can be effective but differences in lifestyle or simultaneity of using different ways such as dieting and doing exercise might be the reason for such differences.

5. Limitations of the Study

The following can be some of the limitations of this study:

Most of the subjects in the sample were not selected randomly and this resulted in the selection of a sample of patients who were not representative of a population of patients with high blood fat. The variables studied were very few and limited so that in some studies different daily, weekly and monthly periods of treatment were reported but the precise amounts of LDL were not mentioned. In some studies, only other medicines were reported but the exact amounts before and after treatment were not reported. In some studies, comparisons regarding the subjects' sex or age were not carried out and data were provided generally. The total rate of LDL reduction through Atorvastatin was reported but comparison among different age groups was not done and individuals at risk were not recognized as belonging to different groups.

6. Conclusion

According to the results of the study Atorvastatin is a medicine in reducing LDL. It reduces the rate of LDL faster and to a larger extent. In addition, the amount of LDL reduction in the elderly and obese people takes place better and quicker than the young and thin individuals. The role of an inappropriate lifestyle such as eating fast food, immobility and lack of physical exercise must not be ignored.

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Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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