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# Impact of Statins Used for Hyperlipidemia on Development of New-Onset Depression and Anxiety: A Prospective Study

Nadiye Karabulut, Seda Ayşe Demirel Dengi, Seçil Arıca

Department of Family Practice, Haseki Training and Research Hospital, Istanbul, Turkey

## ABSTRACT

**Objectives:** Hydroxymethylglutaryl-coenzyme A inhibitors (statins) are used in hyperlipidemia (HL) treatment and are the most efficacious and widely used drug, especially in decreasing low-density lipoprotein cholesterol, have been found to reduce mortality and morbidity in coronary artery disease in a great number of studies. However, the development of depression in patients under statin treatment has been evaluated in very few studies. Thus, this study aims to evaluate the influence of therapy by statin and statin derivatives on anxiety and depression.

**Methods:** This study was a prospective observational study included in patients who were started on statin HL treatment. The patients were found to be administered atorvastatin (10 mg) or rosuvastatin (10 mg) for HL treatment. Those patients were followed up for 10 months. Pre- and post-treatment status of anxiety and depression of the patients was evaluated using the hospital anxiety and depression scale.

**Results:** This study was performed on a total of 219 patients who were diagnosed to have HL. Moreover, 194 (88.5%) and 25 (11.5%) patients were administered atorvastatin and rosuvastatin, respectively. The anxiety score was found 9.0 (5.0–12.0) before the treatment and 8.0 (5.0–12.0) after the treatment ( $p=0.062$ ). In addition, the depression score was found 5.0 (3.0–9.0) before and 5.0 (3.0–9.0) after the treatment ( $p=0.078$ ).

**Conclusion:** Statins are among the most frequently used drug groups for long-term HL treatment. However, this study did not find any significant association between statin therapy and depression or anxiety scores.

**Keywords:** Anxiety, depression, hyperlipidemia



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### Address for correspondence:

Dr. Nadiye Karabulu.  
Department of Family Practice,  
Haseki Training and Research  
Hospital, Istanbul, Turkey

Phone: +90 505 333 41 95

### E-mail:

nadiye\_karabulut@hotmail.com

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## INTRODUCTION

The 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are among the most used drug groups for hyperlipidemia (HL) treatment today.<sup>[1]</sup> They significantly reduce the level of plasma cholesterol by inhibiting the rate-limiting step of cholesterol biosynthesis in the liver and simultaneously increasing the cellular ingestion and catabolism of cholesterol. In addition, serum cholesterol should be lower than the normal population in comorbid conditions, such as diabetes mellitus and coronary artery disease (CAD), and risk-equivalent diseases. Moreover, several studies have demonstrated that statin treatments reduced CAD and associated mortality and morbidity. Furthermore, statins show these cholesterol-lowering effects by invading the cholesterol-binding site on the HMG-CoA reductase enzyme.<sup>[2]</sup>

Statins also inhibited the synthesis of ubiquinone, a mitochondrial respiratory chain enzyme, and their effects on HMG-CoA reductase.<sup>[3]</sup> Moreover, it has shown an inhibitory effect on

the production phase of the energy required for striated muscles and nerve cells with these undesirable side effects. Furthermore, some studies have shown a relationship between low serum cholesterol levels and depression and suicide.<sup>[4,5]</sup>

Considering this information, targeting a continuously lower low-density lipoprotein and cholesterol level has re-awakened the preexisting reliability concerns due to the linear relationship between cholesterol level and CAD mortality.<sup>[6,7]</sup> Cholesterol is a fundamental compound for cell membrane and myelin structure and plays a vital role in the formation, stability, and function of synapses in nerve cells. Thus, it is thought that too much lowering of the cholesterol levels may cause cellular deterioration. The studies conducted had shown that the rate of depression, suicide, and crime increased when the circulating cholesterol level was lowered by diet, medication, or both. Although the cause of this relationship is not fully understood, it has been found that the rate of cholesterol both in the structure of the central nervous system and in cell membranes, as well as the number of serotonin receptors, decreased when the level of cholesterol in the circulation was lowered.<sup>[8]</sup> Thus, it is thought that a relative reduction occurs in the central serotonergic transition, and the efficacy of serotonin that suppresses the harmful behaviours (e.g., suicide and committing a crime) does not occur sufficiently.<sup>[8,9]</sup>

HL is a mostly chronic process, and long-term statins are widely used for its treatment. Thus, the effects, reliability, and well tolerability of statin treatment are essential. This study investigated the effects of statins on depression and anxiety using the hospital anxiety and depression (HAD) scale.

## METHOD

This is a prospective observational study conducted with patients who were initiated on statin treatment with HL diagnosis and followed up between September 2015 and August 2016 in a family medicine clinic. The HAD scale was administered to patients diagnosed with HL at the time of diagnosis and 10 months after starting statin therapy. The age of patients, gender, initiated statin derivative, and body mass index (BMI) were recorded. In addition, the HAD scale was applied by face-to-face interview technique.

The HAD scale was used to investigate the depressive anxiety symptoms. The HAD scale is a reliable and practical assessment scale designed to determine the risk of anxiety and depression and measure its level and intensity change. It was translated by Aydemir et al. into Turkish in 1997, and a validity and reliability study was conducted.<sup>[10]</sup> It includes a total of 14 questions, including anxiety and depression

subscales. Seven of these questions measured anxiety, and the other seven questions measured depression. The lowest score that patients can obtain from both subscales is 0 point, while the highest score is 21 point. The HAD scale has been proven as a useful assessment tool that enables the score ranges to minimize false-positive and false-negative results. No single generally accepted cutoff score was noted for HAD scale. In their original study, Zigmond et al. have recommended two cutoff scores for both scales.<sup>[11,12]</sup> Consequently, a score of 7/8 is for possible depression and a score of 10/11 is for possible anxiety. Scores from 0 to 7 in each subscale are evaluated as "normal", and scores from 8 to 10 are evaluated as "borderline," while scores of 11 and above are evaluated as "abnormal." BMI is a value derived from a person's mass (weight) and height.<sup>[13]</sup> The BMI is defined as the body mass divided by the square of the body height ( $\text{kg/m}^2$ ). Commonly accepted BMI ranges are underweight ( $<18.5 \text{ kg/m}^2$ ), normal weight ( $18.5\text{--}24.9 \text{ kg/m}^2$ ), overweight ( $25.0\text{--}29.9 \text{ kg/m}^2$ ), and obese ( $\geq 30 \text{ kg/m}^2$ ).

Patients who previously used antipsychotic or antidepressant drugs during the study period and patients who used statins and statin derivatives for  $<6$  months were excluded from the study.

The SPSS 15.0 for Windows was used for statistical analysis. Normality was tested using Kolmogorov–Smirnov and Shapiro–Wilk tests. For descriptive results, variables indicated by count were expressed in frequency and percentages, and variables specified by measure were expressed in mean, standard deviation, median, minimum, and maximum. The Wilcoxon signed-rank test was used because the numerical variables were not normally distributed. A  $p$ -value of  $<0.05$  was considered significant.

## RESULTS

The study was included with a total of 219 patients with HL. The mean age of the patients was  $58.5 \pm 6.2$  years, and 147 (67.1%) were females. According to BMI classification, 56 (25.6%) of the patients had normal weight, 115 (52.5%) were overweight, and 48 (21.9%) were obese.

Atorvastatin (10 mg) and rosuvastatin (10 mg) were administered to 194 (88.5%) and 25 (11.5%) patients, respectively. Anxiety and depression scores in the pretreatment and posttreatment are summarised in Table 1.

There was no difference before and after treatment in terms of depression, anxiety, and total HAD score in both women and men ( $p>0.05$ ). Anxiety and depression scores in the pretreatment and posttreatment by gender are summarised in Table 2.

**Table 1.** Anxiety and depression scores in the pretreatment and posttreatment

	Pretreatment	Posttreatment	p
HAD-A	9.0 (5.0–12.0)	8.0 (5.0–12.0)	0.062
HAD-D	5.0 (3.0–9.0)	5.0 (3.0–9.0)	0.078
Total HAD	14.0 (9.0–20.0)	14.0 (8.0–20.0)	0.071

HAD-A: Hospital anxiety and depression–anxiety scale; HAD-D: Hospital anxiety and depression–depression scale.

Data are presented as median (min–max).

Wilcoxon test.

## DISCUSSION

This study found that the patients were administered atorvastatin or rosuvastatin for HL treatment. These patients were followed up for 10 months. Pre- and post-treatment status of anxiety and depression of the patients was evaluated using HAD, and pre- and post-treatment scales were compared. No significant difference was noted in the pre- and post-treatment anxiety and depression rates between the drug groups. Statins are the most preferred group among the lipid-lowering drugs because of their high efficacy, relative reliability, tolerability, and the rate reduction rates of morbidity and mortality related to cardiovascular diseases.<sup>[14]</sup> Statins are among the most frequently used drug groups for the long-term treatment of HL. Although the effects of this group of drugs on the cardiovascular system have been known, the effects of these drugs on other systems, mainly the central nervous system, have also been evaluated. Accordingly, various studies have investigated whether it causes cellular deterioration by lowering the

**Table 2.** Anxiety and depression scores in the pretreatment and posttreatment by gender

	Male	p	Female	p
HAD-A				
Pretreatment	9.0 (5.0–11.0)	0.071	9.0 (5.0–12.0)	0.076
Posttreatment	8.5 (5.0–11.0)		8.0 (5.0–12.0)	
HAD-D				
Pretreatment	5.0 (3.0–9.0)	0.085	6.0 (3.0–9.0)	0.097
Posttreatment	5.0 (3.0–9.0)		5.0 (3.0–9.0)	
Total HAD				
Pretreatment	14.0 (11.0–20.0)	0.140	14.0 (9.0–20.0)	0.083
Posttreatment	14.0 (11.0–20.0)		14.0 (8.0–20.0)	

HAD-A: Hospital anxiety and depression–anxiety scale; HAD-D: Hospital anxiety and depression–depression scale.

Data are presented as median (min–max).

Wilcoxon test.

cholesterol level. In addition, different results have been obtained in studies conducted on the relationship of drugs used in the treatment of HL with depression and anxiety. The animal study of Shrivastava et al. found that the levels of specific ligand binding and G-protein-coupled serotonin 1A receptor, especially in the cell membrane, significantly reduced when the cholesterol level was decreased constantly with mevastatin.<sup>[15]</sup> However, no change was noted in the levels of other cell receptors. This study concluded that G-protein-coupled serotonin 1A receptors in the neural cells might have a role in reducing long-term cholesterol levels by administering statin treatment and the occurrence of anxiety and depression.

In a randomised, double-blind, long-term intervention with pravastatin in ischemic disease study by Stewart RA et al. conducted on CAD patients, the patients were given 40 mg of pravastatin or placebo and followed up for 4 years.<sup>[16]</sup> The patients given the placebo were found to have no change in the serum cholesterol level, while the serum cholesterol level of the patients given pravastatin decreased. However, no difference was noted between the patient groups regarding anxiety and depression. Thus, no significant relationship was concluded between a decrease in serum cholesterol level and anxiety and depression.

The study conducted by Yeh et al. used Taiwan's National Health Insurance Research Database between 2000 and 2010.<sup>[17]</sup> They enrolled two asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) cohorts, one statin and one nonstatin user matched by age, gender, and index date. After adjustment for multiple confounding factors, including age, gender, comorbidities, and medications—statins, inhaled corticosteroids (ICSs), and oral steroids (OSs)—the ACOS cohort with statin use had significantly lower risks of anxiety and depression. However, the ACOS cohort with statin use had lower risks of anxiety and depression, regardless of age, gender, comorbidities, or ICSs and OSs.

In a double-blind clinical study conducted by Muldoon et al., 209 healthy subjects who only had HL were given 20 mg lovastatin or placebo treatment for 6 months and evaluated in terms of depression, neuropsychological status, and quality of life.<sup>[18]</sup> The present study followed the patients diagnosed with HL and initiated statin treatment for 10 months to investigate the relationship between statin use with anxiety and depression. The patients were given 10 mg atorvastatin or 10 mg rosuvastatin as treatment, and both their pre- and post-treatment anxiety and depression levels were determined by the HAD scale. As a result, there is no significant difference between HAD anxiety and depression scores before and after statin therapy.

In a randomised controlled study conducted by Morales et al. on an elderly volunteer group with HL, 39 and 33 patients were initiated on placebo and 20 mg simvastatin treatment, respectively, and followed up for 15 weeks.<sup>[19]</sup> The cholesterol levels were lower in the simvastatin group. Still, more depression symptoms were seen, and the symptoms of positive mood decreased when both of the groups were compared after the treatment. The majority of the patient groups in the current study were composed of middle-aged and elderly patients. Elderly patients mainly were found to have a chronic disease and use multiple medications. Still, no significant difference was noted in the pre- and post-treatment anxiety and depression rates among the patient age groups. The patients using atorvastatin and rosuvastatin, two of the most used statins currently, were included in the current study. Other statins were not included due to their limited use in the tiny fraction of the population.

The present study has several limitations. One of the limitations was the number of patients. The duration of patient follow-up in the study groups was insufficient to reveal the relationship between statin use and the development of depression and anxiety. Other limitations were that not all statin group drugs were included in the study, the group of patients in the study was small, and the follow-up time was short.

## CONCLUSION

The relationship between the use of statin with anxiety and depression was investigated in the current study. As a result of this study, no significant relationship was found between statin use and anxiety and depression scores. It may be beneficial to conduct multicenter studies with longer follow-up and larger patient groups.

## Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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**Ethics Committee Approval:** This study was approved by the Ethics Committee of the Haseki Training and Research Hospital (Approval date: Oct 15, 2015, and Approval number: 259). In addition, the participants were informed about the study, and individual informed consent was obtained according to the principles of the Declaration of Helsinki.

**Authorship Contributions:** Concept – N.K.; Design –N.K.; Supervision – N.K., S.A.; Materials – N.K.; Data collection and/or processing – N.K.; Analysis and/or interpretation – N.K., S.A., D.D.; Literature search – N.K.; Writing – N.K.; Critical review – N.K., S.A.

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