ORIGINAL PAPER

J Health Inequal 2023; 9 (2): 217–223

Submitted: 26.11.2022; accepted: 30.04.2023

DOI: https://doi.org/10.5114/jhi.2023.131805

JOURNAL of Health Inequalities

The effect of statins intake on sleep quality

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ABSTRACT

Introduction: It is hypothesized that statin therapies might be connected with an increased risk of sleep disturbances. The objective of the study was to examine the association between use of statins (atorvastatin and rosuvastatin) and the risk of sleep disturbances compared with a group of patients who do not receive statin therapy. Additionally, we compared the effect of atorvastatin and rosuvastatin on sleep quality.

Material and methods: We examined 135 patients (62 males, 73 females, mean age: 71.1 ± 10.2) with indications for chronic statin therapy (85 patients taking atorvastatin, 50 patients taking rosuvastatin) and 65 individuals without statin therapy as the control group (23 males, 42 females, mean age: 65.8 ± 11.6). The effect of statin on sleep parameters was assessed using the Athens Insomnia Scale (AIS), the Pittsburgh Sleep Quality Index (PSQI), and the Insomnia Severity Index (ISI). The exclusion criteria were use of hypnotic drugs, obstructive sleep apnoea, decompensated heart failure, and prostatic hyperplasia.

Results: Our results showed that patients during atorvastatin or rosuvastatin therapy obtain a significantly higher number of points in the following: AIS compared to the control group ($p < 0.001$, $p < 0.01$), PSQI compared to the control group ($p < 0.001$), and ISI compared to the control group ($p < 0.001$, $p < 0.05$). Patients during atorvastatin or rosuvastatin therapy obtain a significantly higher number of points in the AIS in the first 5 questions about sleep-related symptoms compared to the control group.

Conclusions: This study indicated that patients taking atorvastatin or rosuvastatin reported sleep disturbances more often than patients without statin therapy.

KEY WORDS: rosuvastatin, atorvastatin, sleep disorders, insomnia scales.

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INTRODUCTION

Statin therapy is a basis for the primary and secondary prevention of cardiovascular diseases. Drugs administered in this group of diseases account for approximately 37.5-48.6% of the total number of administered drugs in the population [1, 2].

As a result of a large number of studies and meta-analyses, statins seem to be safe and well tolerated by patients [3-6]. According to experts, total statin intolerance, which requires withdrawal of a statin, affects < 5% of patients with symptoms of statin intolerance [7, 8]. Statin therapy is fraught with a low risk of side effects. Statin-related side effects include muscle pain (3-5%), myopathy (0.1-0.2%), hepatotoxicity (< 1%), and prodiabetogenic effects (9-27%) [9, 10].

The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) consensus "Adverse Effects of Statin Therapy" emphasized there is no evidence that long-term statin use negatively affects cognitive function, contributes to cataracts, or increases the risk of haemorrhagic stroke in people without cerebrovascular disease [10, 11].

A U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) analysis showed that people on statin therapy reported abnormalities during sleep such as increased time needed to fall asleep, more frequent nocturnal awakenings, and parasomnias [12]. Some studies indicate that statins can cause sleep disorders, which can be manifested by nightmares, hallucinations, and insomnia [13, 14]. Furthermore, people requiring statin therapy were more likely to use hypnotic drugs [12]. However, neither the ESC nor EAS has presented their opinion on the effect of statin use on sleep disorders [11].

Sleep disorders are a problem especially in the elderly, in whom they can affect not only the quality of life but can also have negative health consequences, such as weight gain or insulin resistance [7]. It is suggested that the use of statins with a high degree of lipophilicity may be associated with frequent occurrence of central nervous system disorders compared to hydrophilic statin therapy. Hydrophilic statins (rosuvastatin and pravastatin) appear to induce fewer symptoms of statin intolerance, which is especially important in elderly patients [15, 16].

The introduction and use of standardized scales of subjective sleep quality assessment such as the Pittsburgh Sleep Quality Index (PSQI), the Athens Insomnia Scale (AIS), and the Insomnia Severity Index (ISI) allow us to assess sleep quality disorders and can be a useful tool for monitoring the safety of statin therapy.

The aim of the study was to assess the association between use of statins (atorvastatin and rosuvastatin) and the risk of sleep disturbances compared with a group of patients not receiving statin therapy. Additionally, we compared the effect of atorvastatin and rosuvastatin on sleep quality.

MATERIAL AND METHODS

The study included 200 patients (85 males and 115 females, mean age: 69.4 ± 11 years) hospitalized in the Department of Internal Medicine and Clinical Pharmacology of the Wladyslaw Bieganski Hospital in Lodz in the years 2016-2018. The study group consisted of 135 people (62 males and 73 females, mean age: 71.1 ± 10.2 years) requiring chronic statin therapy, of whom 50 patients took rosuvastatin (RP) and 85 took atorvastatin (AP). The control group (CG) consisted of 65 people (23 males and 42 females, mean age: 65.8 ± 11.6 years) who were not administered drugs.

Patients qualified for the control group did not have indications for statin therapy, in the future we will want to conduct an analysis with patients who have indications for statin therapy and do not take the drug.

While analysing the group of patients included in the study, we could not modify the chronic pharmacotherapy.

PATIENT SELECTION CRITERIA

Criteria for inclusion in the study: informed consent of the patient, chronic (> 3 months) intake of atorvastatin or rosuvastatin, and age > 18 years.

Criteria for exclusion from the study: prostatic hyperplasia, sleep apnoea syndrome, decompensated heart failure, decompensated diabetes, acute coronary syndrome, cerebrovascular disease, transient ischaemic attack in the last 3 months, hospitalization due to a surgery or acute, severe illness, active or past cancer, depression, Parkinson's disease, Alzheimer's disease, and MMSE score < 24.

We excluded patients with decompensated diabetes type 2 from the study due to the effect of the symptoms of decompensated diabetes on sleep quality. We did not include patients with pre-diabetes.

This study did not analyse the effect of physical activity on sleep quality. The patients enrolled in the study were fully independent with no restrictions in daily physical activity.

DESCRIPTION OF LIPID PROFILE ASSESSMENT

The lipid profile in the serum of patients chronically using statins and in the control group was determined using the colorimetric assay. The lipid profile included total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

SCALES AND QUESTIONNAIRES

Sleep quality was examined using scales and questionnaires applicable in the diagnostics of sleep disorders.

The Athens Insomnia Scale evaluates the quality of sleep and the quality of the following day. A score equal to or higher than 8 indicates insomnia [17].

The Pittsburgh Sleep Quality Index assesses the following components of sleep quality, i.e. subjective sleep quality, duration of sleep, and ability to function during the day. The total number of points obtained is interpreted as poor sleep quality (score > 5) or good sleep quality (≤ 5) [18].

The Insomnia Severity Index assesses the severity of both nighttime and daytime components of insomnia. Achieving ≥ 14 points indicates insomnia [19].

Cognitive skills were assessed using the revised Mini-Mental State Examination (MMSE). A score < 24 points is identified as dementia, 24–26 points as mild cognitive impairment, and > 27 points as normal.

STATISTICAL ANALYSIS

The obtained data were subjected to a statistical analysis. The results were expressed as the average value ± the standard deviation (for quantitative variables) and the structure of the indicator (for qualitative variables). Statistical significance between the 2 groups was determined using the nonparametric Mann-Whitney test. A p-value < 0.05 was considered statistically significant. The χ^2 independence test was used to compare qualitative variables; in the case of non-compliance with assumptions of this test, the exact Fisher test was used.

All analyses were performed using STATISTICA v 12.5 (StatSoft, Inc., Krakow, Poland).

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study received a positive opinion of the Bioethics Committee of the Medical University of Lodz: Consent number RNN/148/18/EC of 12.06.2018.

TABLE 1. Characteristics of the study group

Parameter	Control group $n = 65$	Patients $n = 135$		p-value
Age [years]	65.8 ± 11.6	71.1 ± 10.2		ns
Patients > 65 years old	58%	70%		ns
Males/females	23/42	62/73		ns
Mean score of MMSE	27 ± 3.3	26.3 ± 3.2		ns
Statin	–	Atorvastatin: 85	Rosuvastatin: 50	ns
Mean dose of statin [mg]	–	23.2 ± 13.0	15.1 ± 8.8	–
Length of therapy [years]	–	6.2 ± 4.3	2.8 ± 1.6	–
Mean age [years]	–	72.1 ± 10.3	69.3 ± 9.8	–
Sex	–	M: 41, F: 44	M: 21, F: 29	–
Total cholesterol [mg/dl]	181.4 ± 40.7	161.9 ± 50.0	162.1 ± 51.2	< 0.05
LDL [mg/dl]	101.0 ± 30.9	89.5 ± 38.4	85.8 ± 37.5	< 0.05
HDL [mg/dl]	50.0 ± 14.8	44.3 ± 14.2	44.7 ± 18.3	< 0.05
TG [mg/dl]	123.5 ± 45.4	129.5 ± 72.5	117.9 ± 69.8	ns
Arterial hypertension	55%	87%	84%	ns
Coronary heart disease	45%	57%	60%	ns
Diabetes mellitus	12%	38%	28%	ns

ns – not significant, MMSE – Mini-Mental State Examination, LDL – low-density lipoprotein, HDL – high-density lipoprotein, TG – triglycerides, TC – total cholesterol

All participants received study material informing about the study objectives, the voluntariness of participation, and data protection. All participants gave written consent prior to their participation.

RESULTS

The study group consisted of 135 people (62 males and 73 females, aged between 45 and 90 years; mean age: 71.1 ± 10.2 years) who had been administered a statins for at least 3 months. Of this number, 50 patients took rosuvastatin (RP) and 85 patients took atorvastatin (AP). Doses of rosuvastatin ranged between 5 and 40 mg (mean 15.1±8.8 mg), and atorvastatin between 10 and 80 mg (mean 23.25 ± 13 mg). Patients > 65 years of age accounted for 70% of the entire group who had been taking statins for at least 3 months. The average Mini-Mental State Examination (MMSE) score equalled 26.3 ± 3.2.

The control group (CG) (i.e. not taking statin drugs) consisted of 65 people (23 males and 42 females, aged between 45 and 90 years; mean age: 65.8 ± 11.6). Patients aged > 65 years accounted for 58% of the non-statin group. The average score on the Mini-Mental State Examination (MMSE) was 27 ± 3.3.

Patients took atorvastatin and patients took rosuvastatin demonstrated significantly lower levels of total cholesterol (161.9 ± 50 atorvastatin and 162.1 ± 51.2 rosuvastatin) compared to the CG (181.45 ± 40.7), $p < 0.05$ and low-density lipoprotein (LDL) cholesterol levels (89.5 ± 38.4 atorvastatin and 85.8 ± 37.5 rosuvastatin) compared to the CG (101 ± 30.9), $p < 0.05$. High-density lipoprotein (HDL) cholesterol levels were significantly lower in the AP compared to RP and in the CG ($p < 0.05$). Triglycerides (TG) values did not differ significantly between the groups. There was no difference in LDL cholesterol concentration in patients chronically using atorvastatin or rosuvastatin.

The age difference was not significant between the AP (72.1 ± 1) and RP (69.3 ± 9.8) therapy compared to the CG 65.8 ± 11.6, $p > 0.05$ (Table 1).

EFFECT OF ATORVASTATIN AND ROSUVASTATIN ON THE AIS COMPARED TO THE CONTROL GROUP

Patients took atorvastatin or patients took rosuvastatin scored significantly higher on the AIS 10.3 ± 4.7 vs. 6.7 ± 2.9 ($p < 0.001$), respectively; 9.1 ± 4.4 vs. 6.7 ± 2.9 ($p < 0.001$) (Figure 1A). AP or RP therapy scored significantly higher on the AIS in the first 5 questions about symptoms that occur at night compared to the CG of 6.4 ± 3.3 ($p < 0.001$) 5.3 ± 3.1 ($p < 0.05$) vs. 3.7 ± 2.3, respectively (Figure 1B).

EFFECT OF ATORVASTATIN AND ROSUVASTATIN ON THE PSQI COMPARED TO THE CONTROL GROUP

Patients took atorvastatin or patients took rosuvastatin scored significantly higher in the PSQI compared to the CG of 8.9 ± 3.9, respectively; 8.4 ± 4.6 vs. 6.2 ± 3.3, $p < 0.001$ (Figure 2).

EFFECT OF ATORVASTATIN AND ROSUVASTATIN ON THE ISI COMPARED TO THE CONTROL GROUP

Patients took atorvastatin or patients took rosuvastatin scored significantly higher in the ISI compared to the CG 11.0 ± 5.5 vs. 7.1 ± 3.7 ($p < 0.001$), respectively; 9.3 ± 5.3 vs. 7.1 ± 3.7 ($p < 0.05$) (Figure 3).

EFFECT OF ROSUVASTATIN AND ATORVASTATIN ON SLEEP QUALITY

Patients taking 20 mg of rosuvastatin ($p < 0.05$) received more points on all scales assessing sleep quality disorders. There was no relationship between the dose of atorvastatin (20 mg and 40 mg), the dose of rosuvastatin (10 mg), and the number of points obtained on scales assessing sleep quality disorders (Table 2).

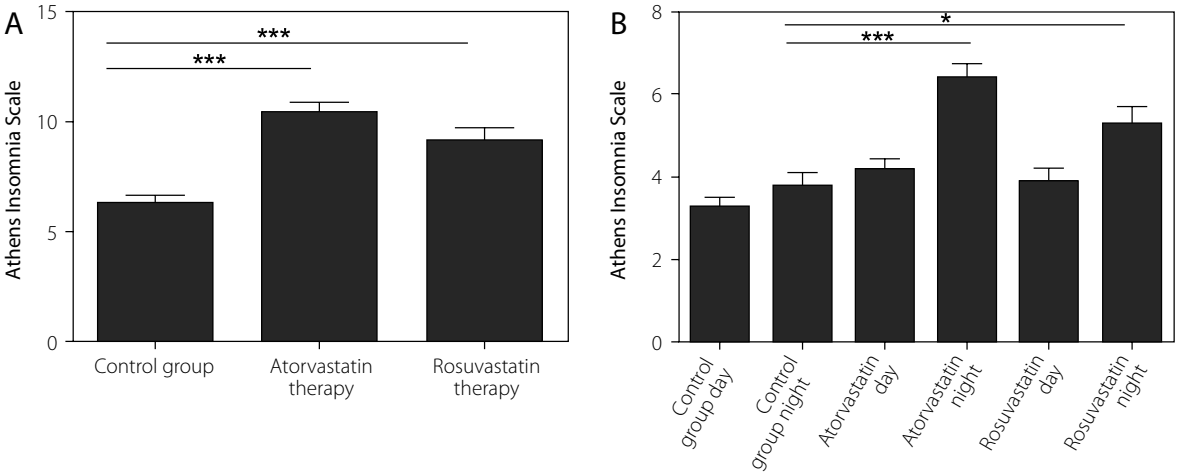

FIGURE 1. A) Comparison of the number of points obtained on the Athens Insomnia Scale (AIS) in the group of atorvastatin therapy (AP) and rosuvastatin therapy (RP), ***$p < 0.001$ (Mann-Whitney *U*-test). B) Comparison of the number of points obtained on the AIS during the day and during the night, *$p < 0.05$, ***$p < 0.001$ (Mann-Whitney *U*-test)

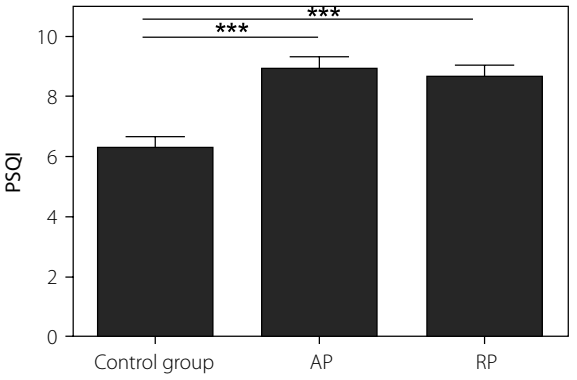

FIGURE 2. Comparison of Pittsburgh Sleep Quality Index (PSQI) scores in patients took atorvastatin (AP) and patients took rosuvastatin (RP), ***$p < 0.001$ (Mann-Whitney *U*-test)

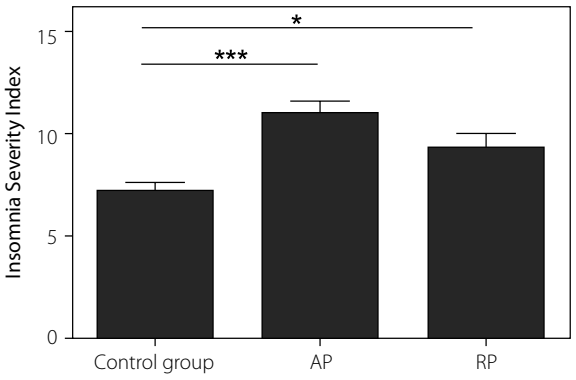

FIGURE 3. Comparison of Insomnia Severity Index (ISI) scores in patients took atorvastatin (AP) and patients took rosuvastatin (RP), *$p < 0.05$, ***$p < 0.001$ (Mann-Whitney *U*-test)

TABLE 2. Comparison of the dose of atorvastatin and rosuvastatin on scales assessing sleep disorders

Sleep scales	Dose of statin					
	Atorvastatin		*p*-value	Rosuvastatin		*p*-value
	20 mg	40 mg		10 mg	20 mg	
Mean score of AIS	10.7 ± 4.2	10.4 ± 4.6	ns	7.9 ± 3.5	11.0 ± 5.0	< 0.05
Mean score of PSQI	8.9 ± 3.7	9.1 ± 3.8	ns	8.0 ± 4.0	9.9 ± 5.0	< 0.05
Mean score of ISI	11.6 ± 4.6	11.3 ± 5.3	ns	8.5 ± 4.5	11.2 ± 5.3	< 0.05

ns – not significant, AIS – Athens Insomnia Scale, PSQI – Pittsburgh Sleep Quality Index, ISI – Insomnia Severity Index.

DISCUSSION

Statins are drugs commonly applied in the treatment of hypercholesterolaemia. Generally, they are well tolerated and rarely induce side effects (which mainly affect muscles [pain, weakness, and fatigue], liver, and kidneys) [9, 10]. The literature shows, however, that certain statins (lovastatin, simvastatin, rosuvastatin) may be associated with an increased risk of sleep disorders [20, 21].

The quality of sleep in this study was assessed using scales and sleep questionnaires (subjective methods): AIS, ISI, and PSQI. Our study revealed that patients taking atorvastatin or rosuvastatin scored significantly higher on all sleep scales than patients who did not receive statin treatment. Additionally, AIS showed that these disorders caused significantly higher levels of daytime sleepiness more often than in control patients. It should be emphasized that the PSQI and AIS scales complement the results of polysomnography [18, 22, 23]. The available literature proves that subjective methods present a sensitivity between 73.0% and 97.7%, while their specificity ranges in the interval 50-96%. Objective methods such as actigraphy or polysomnography present a sensibility higher than 90%. However, their specificity is low compared to their sensitivity, being one of the limitations of such technology. The factors such as the patient's perception of her or his sleep can be provided only by subjective methods [24].

The conclusions that we drew from our work correspond to those included in the European MHRA review. It assessed evidence of adverse effects associated with the use of statins and showed negative effects of all statins on sleep disorders [25]. Similar conclusions were presented by the US Food and Drug Administration (FDA), which revealed a link between statin use and sleep disorders. The FDA confirmed the occurrence of insomnia in patients who were administered 40 mg of atorvastatin (5.3% vs. 2.9% in the placebo group) [26, 27]. Takada *et al.* in an analysis of the FDA database: FAERS (US Food and Drug Administration [FDA] Adverse Event Reporting System [formerly AERS)]) and JMIRI (Japan Medical Information Research Institute, Inc., Japan) claim that statins, regardless of lipophilicity, induce insomnia. In his analysis, he emphasized that there is no evidence implying that hydrophilic statins reduce the risk of insomnia [12]. On the other hand, there are some reports confirming that use of rosuvastatin causes disturbances in the initiation and maintenance of sleep and parasomnia [20, 21].

Sierra *et al.*, in contrast, believe that the nature of statins (their lipophilicity) probably plays a significant role in the occurrence of sleep disorders. Their ability to cross the blood-brain barrier is one of the primary factors contributing to the above disorders. The greatest potential in this regard is shown by simvastatin (33%) and fluvastatin (28%), intermediate potential is shown by pitavastatin (13%) and lovastatin (11%), and the lowest by atorvastatin (5%), rosuvastatin (0%), and pravastatin (0%) [28]. These conclusions are confirmed by the work of Schaefer *et al.*, who confirmed that sleep disorders were more likely to occur after administration of lovastatin (reduction of sleep duration by 18%) rather than pravastatin [29]. In a similar study, Vgontzas *et al.* showed an adverse effect of lovastatin compared to pravastatin, which manifested as waking immediately after falling asleep [15].

Broncel *et al.* in their meta-analysis emphasize that it is debatable whether statins, which are capable of crossing the blood-brain barrier, can cause sleep disorders [30]. Harrison *et al.* presented similar conclusions. In their work, they showed no association between statins crossing the blood-brain barrier and sleep disorders. There were no significant differences in a 4-week follow-up in patients receiving 40 mg of simvastatin or 40 mg of pravastatin compared to the placebo group [31].

In contrast, Tuccori and Galatii indicate that very often the conversion of a lipophilic statin to a hydrophilic enables the elimination of sleep disorders [32, 33]. Engelberg drew similar conclusions and highlighted the fact that statins with a higher degree of lipophilicity adversely affect the central nervous system [34].

The results of a 6-month follow-up in a randomized double blind placebo-controlled trial conducted by Golomb *et al.* indicate that patients taking simvastatin in a dose of 20 mg reported sleep problems much more frequently and statin therapy significantly worsened sleep quality compared to pravastatin administered at a dose of 40 mg or placebo. Additionally, no significant difference was observed between pravastatin and placebo intake regarding sleep disorders [35].

The most common side effect of statin therapy is muscle pain. A study by Ehlen *et al.* suggests that disturbances in skeletal muscle metabolism can lead to changes in sleep. This has been linked to a knockout of the BMAL1 gene in skeletal muscle. It has been established that the expression of BMAL1 in muscles is a key element in sleep regulation [36]. Additionally, Ehlen *et al.* speculate about the role of the peptide irisin, a factor of muscle origin that can affect brain function, and the peroxisome proliferator-activated gamma receptor coactivator 1-α (PGC-1α), which stimulates the release of irisin into the bloodstream [36]. Importantly, Ehlen *et al.* emphasize that their study does not clearly identify the mechanisms driving changes in BMAL1 expression. The relationship between statins and BMAL1 is poorly understood [36].

In a study by Stroes *et al.* concerning the effect of lipophilic simvastatin and hydrophilic rosuvastatin on muscle cells, simvastatin has been shown to have a significant effect on the expression in the muscle cells and the secretion of ω-3 and ω-6 eicosanoids and prostaglandins at higher levels [37]. This is associated with an increase in the intensity of the transformation of omega-n fatty acids in the muscles, which in turn causes a deterioration of the regenerative potential. This could be in part due to the prostaglandin depletion within the muscle, given that prostaglandin E_2 (PGE_2), which is synthesised from

arachidonic acid, is responsible for muscle stem cell proliferation in response to injury [38]. This damaging effect on the muscles will lead to painful musculoskeletal sensitisation, which has been linked to worse sleep quality [39, 40]. Stroes *et al.* also indicate that muscle damage by statins is associated with increased serum prostaglandins, which may mildly promote sleep via the EP4 receptor in the brain [41]. Another product of the arachidonic acid metabolism, prostaglandin D2 (PGD2), is also a well-known factor influencing sleep [42]. Some studies indicate that prostaglandin D_2 is the most effective eicosanoid sleep promoter [42].

Our study showed that statins, regardless of lipophilicity, induce sleep disorders manifested by insomnia. In addition, patients taking hydrophilic rosuvastatin at a dose of 20 mg appeared to receive higher scores on all scales in comparison to a dose of 10 mg.

The cause of insomnia in older age is most often secondary, associated with chronic diseases or psychosocial factors [43]. Forty-three per cent of the respondents of an EPESE study (Established Populations for Epidemiologic Studies of the Elderly), conducted on more than 9000 outpatients over 65 years of age, demonstrated difficulty falling asleep or maintaining sleep. The sleep disorders were exacerbated in people with worse health and those taking multiple medications. The problem was more common in women, mainly those with depression and respiratory diseases [44]. In our study, patients > 65 years of age represented 70% of the group chronically (for more than 3 months) using a statin and 58% of the entire control group. No statistical significance was obtained in patients below or above 65 years of age. Cognitive function did not differ significantly between the study and control groups.

There are no conclusive studies that confirm that statins negatively affect sleep quality or worsen the next day's well-being. Swiger's extensive analysis summarized the effects of statins on sleep and physical function. The author concluded that the evidence of negative effects of statins is insufficient and biased [45]. In contrast, Szmyd *et al.* in their work highlighted the fact that sleep disorders induced by statin administration are understudied and require more research [46].

STUDY LIMITATIONS AND STRENGTHS

Our study has some limitations. Firstly, the study group included a small number of patients on low doses of statins (5-10 mg) and very high doses (40-80 mg). Secondly, there was a lack of assessment of sleep disorders using objective methods such as polysomnography or actigraphy.

The strenghts of the study: 1) There are limited data on the influence of statins on sleep quality in patients with lipid disorders. 2) The important strength of our study is that we compared the effect on sleep quality of the 2 most potent and most frequently used statins. Such a comparison had not been performed previously. 3) In this study, to assess the quality of sleep we used methods including scales and questionnaires applicable in the diagnostics of sleep disorders (subjective methods). The factors such as the patient's perception of her or his sleep can be provided only by subjective methods.

CONCLUSIONS

The present results indicated that higher doses (20 mg) of hydrophilic statins (rosuvastatin) are more likely to cause sleep disorders than lower doses (10 mg). Statins, regardless of lipophilicity, are associated with sleep disorders and induce insomnia. The study also showed that patients taking atorvastatin or rosuvastatin for more than 3 months reported inferior quality of the night compared to the quality of the day on the AIS.

DISCLOSURE

The authors report no conflict of interest.

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AUTHORS' CONTRIBUTIONS

KT, MS, MB, PGP prepared concept and design. KT, MS, PGP collected and analysed data. KT wrote the article. All authors read and approved the final version of the article. PGP critically revised it.