

Intensity and frequency of musculoskeletal pain among statin and non-statin taking patients referred to physical therapy - A cross sectional survey

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Abstract

Objective: To evaluate the intensity and frequency of musculoskeletal pain among patients who attended physical therapy (PT) clinics and take statins.

Design: A cross-sectional survey.

Setting: Five outpatient PT clinics in one Health Maintenance Organization in Israel.

Participants: Patients over 40 years old with musculoskeletal pain who applied for PT. Statin therapy was considered if given for a period of over two months. Patients with other diseases that could cause musculoskeletal pain were excluded.

Main outcome measures: Musculoskeletal pain was evaluated by the Modified Nordic Musculoskeletal Questionnaire. Data on statin intake and type, treatment duration, cardiovascular diseases, other medication, and demographic variables were collected by personal interviews and medical records.

T and Chi²-tests evaluated differences between continuous and categorical variables, respectively. Regression logistic analysis evaluated the contribution of independent variables to musculoskeletal intensity and frequency.

Results: Patients who attended PT and took statins had a higher frequency of musculoskeletal pain in multiple body sites, more frequent pain in the past year and higher pain intensity over the past week compared to non-statin taking patients. There was a significant positive correlation between pain frequency and intensity ($r=0.64$, $p < 0.05$) and negative correlation between pain intensity and physical activity ($r=-.16$, $p < 0.05$).

Conclusions: Patients who attend PT clinics and take statins suffer from higher severity and frequency of musculoskeletal pain compared to patients who attended PT and do not take statins. These results should be taken in account during patient physical assessment and PT intervention.

Abbreviations: BMI: Body Mass Index; MNMQ: Modified Nordic Musculoskeletal Questionnaire; HMO: Health Maintenance Organization; CK: Creatine Kinase; PT: Physical Therapy.

Introduction

The use of statins to reduce low-density cholesterol is widespread worldwide for prevention and treatment of cardiovascular diseases and considered to be the first-line therapy for hypercholesterolemia [1-4]. About 25 million people worldwide use lipid-lowering drugs on a regular basis [1,2] and about 19% of the population of Israel [5,6]. Statins drugs (LDL-C) inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which is responsible for the rate of cholesterol synthesis [7]. They have been shown to reduce morbidity and mortality associated with cardiovascular disease [8,9].

Although statins are generally well tolerated, musculoskeletal side effects may arise and are commonly reported among those treated [1-3]. In rare cases, potentially life-threatening statin-induced rhabdomyolysis may occur, a condition characterized by acute muscle damage resulting in elevation of creatine kinase (CK) levels, possible renal failure, and even death [3-10]. The evidence on the relationship between musculoskeletal pain and statin consumption is controversial. Some

studies showed that statin use is associated with greater incidence of musculoskeletal pain [1,2,11] while other did not [12-14]. For example, in a cross-sectional study of 3,580 adults over age 40 in the US, 11.2% took statins and 22% of them reported having had musculoskeletal pain in at least one anatomic region over the last 30 days, compared with 16.7% of those not taking statins ($P=0.01$). Statin users were older, more likely to be male, former smokers, and reported poor/fair health status [1]. The most common regions associated with musculoskeletal pain were lower extremities and lower back [1,11]. However, a Dutch study of adults aged 75 and older did not find significant difference in musculoskeletal pain between the statin users and nonusers (3.3% vs 2.5%) [14]. Similar results emerged after adjustment for age, sex and exclusion of participants with rheumatic diseases. The authors raised a possibility that the results are underestimation of the association between statin use and muscle complaints and that the validity of the

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measure to assess musculoskeletal pain was not satisfactory. Similarly, according to a systematic literature review of 35 double-blind clinical trials, statin therapy was not a risk factor for musculoskeletal pain [12]. Another systematic review of 42 studies with placebo and statin treatment groups examined how musculoskeletal pain is evaluated and why there is a difference in the outcome of clinical studies and the results of the observational studies [13]. Patients were monitored for at least six months in all studies. The authors aligned with previous findings [12,14] and found a low percentage of musculoskeletal pain, with no significant difference between the statin and placebo group. They added that the variance is sometimes due to different research methods that may influence data collection and to different characteristics of the participants included in the studies.

In several studies, the relationship between the type of statin and the incidence of musculoskeletal pain has also been examined [12]. The highest percentage of musculoskeletal pain was found in patients receiving atorvastatin without increase in CK enzyme. Similarly, the conclusions of a literature review and meta-analysis that included 18 controlled clinical trials found that patients receiving atorvastatin had higher rates of musculoskeletal pain, followed by treatment with simvastatin and pravastatin, with a similar chance of hydrating musculoskeletal pain [15]. Of the different types of statins, only the four types mentioned above are marketed in Israel.

One of the challenges researchers face when testing drug use is the reliability of patient's self-report which is very common [16-21]. Self-reports are subject to errors and biases due to lack of familiarity with medication names, recall bias, and sometimes patients may be less willing to disclose details of certain drugs than others, such as depressants or mood stabilizers [16,17]. Self-report can be validated by comparison to a more reliable measure such as a medical record, although there is no agreement on "gold standard" for this topic [17,18]. However, the results of a cohort study showed a very good match between self-report and data in the medical record [19]. In that study, a multivariate logistic regression, found that variables such as intelligence, education, age, or gender did not predict poor drug use reporting compared to medical record documentation. In contrast, in two other studies, the authors concluded that the use of self-report questionnaires is not accurate enough for testing compliance [20,21].

Most surveys conducted so far included participants from the general population who differed in their characteristics from the population attending physical therapy (PT), of whom the majority complain of musculoskeletal pain. The relationships between musculoskeletal pain and statin in these patients is unknown. A positive relationship between statin therapy and the intensity and frequency of musculoskeletal pain may deserve new attention in the assessment and treatment of these patients. In addition, in most of the previous studies, the incidence of musculoskeletal pain was examined according to participant reports of the existence of this problem with a 'yes' or 'no' answer. This dichotomic measurement is insensitive and does not address the intensity and frequency of participant complaints, although perception of pain is subjective and may vary among participants.

Therefore, the objectives of the present study are: 1. To evaluate the intensity and frequency of musculoskeletal pain reported by patients who attended PT taking and not taking statins; 2. To evaluate the relationship between those patient's demographic and health characteristics and musculoskeletal pain; and 3. To evaluate the relationship between type of statin and intensity and frequency of musculoskeletal pain. The study hypotheses were: 1. Intensity and

frequency of musculoskeletal pain in patients receiving PT is higher among statins users than among non-statin users. 2. There is a positive relationship between the intensity and frequency of musculoskeletal pain and statin therapy, cardiovascular disease, smoking, age, body mass along with the use of other medications and adverse physical activity. 3. There is a difference between the intensity and frequency of musculoskeletal pain between patients on various types of statin drugs.

Methods

Study design and participants

A cross-sectional survey was conducted among patients who applied for treatment at five PT clinics in the years 2018-2019. The included subjects were women and men over 40, who applied for PT at one of the five clinics, with complaints of musculoskeletal pain in various body parts. Subjects were excluded if they also had diseases known to increase the risk of musculoskeletal pain such as active cancer, rheumatic and neurological, diseases, underwent orthopedic surgery in the past year, fibromyalgia, and were pregnant. The sample size was calculated considering that 19% of the total population is treated with statins [5]. A medium effect size required a sample of 186 patients, of which 30 were patients who use statin. The Helsinki Commission of a Meuhedet Health Services approved the study (application number 03-28-02-18). Patients gave informed consent to be interviewed and to retrieve data from their medical records. A pilot study was carried out to evaluate the validity of drug self-reporting (Appendix 1).

The dependent variables were: 1. Intensity and frequency of musculoskeletal pain evaluated by the Modified Nordic Musculoskeletal Questionnaire (MNMQ) [23,24]. The MNMQ Hebrew version has good reliability (Kappa=0.76 -1.0, ICC=0.9) [25]. The questions referred to the existence of musculoskeletal pain in the neck, shoulders, upper / lower back, elbows, wrist, forearm, arm, hips, knees, and ankles. The average number of sites was calculated for data analysis. Pain intensity was evaluated by the question: "What is the intensity of pain you feel during the last 7 days?" A corresponding number from 0 to 10 was used, with 0 'no pain at all' and 10 'very strong pain'. The incidence of musculoskeletal pain was evaluated by dichotomous 'yes' / 'no' answers. Pain frequency was evaluated on a five-degree Likert type scale by the question: "How often do you experience pain?" (1- One-time event, 2- Rarely, 3- Sometimes, 4- Often, 5- All the time). Work disturbance was evaluated by a dichotomous question: "Has the problem / pain over the past three months bothered your work?"

Main outcome measures

The main independent variable was statin medication intake. Statin therapy was considered when used for at least two months because side effects of musculoskeletal pain usually begin 4-6 weeks after starting treatment [26]. Duration of treatment was determined by months. Participants were asked to mark the drugs they use from a list of generic or commercial names (Appendix 2). It was validated by information from their medical records. Other independent variables were age, gender, body mass index (BMI), physical activity, smoking, and additional medication. The level of physical activity was measured according to the World Health Organization's definition [27]. It refers to the last 30 days and divided into three categories as follows: vigorous exercise: moderate exercise and 3. Little-to-no physical activity (Appendix 3).

Smoking was defined as a dichotomous variable, yes / no when patients who answered yes were asked to indicate how many cigarettes a day, they usually smoke.

The list of additional drugs that may increase the risk of musculoskeletal pain included:

1. Drugs affected by the pharmacokinetic mechanism and inhibit the CYP3A4 enzyme responsible for the metabolism of statins (e.g. Antifungal drugs: itraconazole, ketoconazole, voriconazole and Macrolide family antibiotics: clarithromycin, erythromycin);
2. Immunomodulatory drugs such as cyclosporine and HIV treatment drugs like Atazanavir, Darunavir, Elvitegravir/Colbistat, Fosamprenavir, Indinavir, and Lopinavir; and
3. Pharmacodynamic mechanisms such as Prednisone (Steroid), Blood Pressures (e.g. Verapamil, Amlodipine), and Arrhythmias: Amiodarone (Procor) and Dronedarone.

Statistics

T and Chi² tests were used to evaluate differences between continuous and categorical variables, respectively. Pearson correlation evaluated the relationship between the dependent variables and the independent dichotomous variables (statin taking, cardiovascular disease, smoking, and additional medication). One-way variance analyses evaluated the relationship between the dependent variables and type of statin. Multiple logistic regression evaluated the contribution of the independent variables to the binary dependent variable. The data analysis was performed by SPSS 23.0 software.

Results

Of 187 patients who were interviewed 164 met the inclusion criteria. Nineteen didn't meet the inclusion criteria and three stopped the interview when they were asked about their medical history. Of the eligible patients 40.85% took statins, three-quarters were women and the average age was 59.7 years. Patients who took statins were older and less engaged in physical activity compared to those who did not. No differences were found between the groups in terms of gender, smoking habits, and BMI (Table 1).

Statin users reported pain at more sites, exacerbated pain in the past year, and higher pain intensity over the past week compared to patients who do not take statins. In addition, statin users had more work disruption in the past three months compared to non-statin users (Table 2). There was a positive correlation between pain frequency and pain intensity (r=0.64). In addition, low but statistically significant correlations were found between pain frequency and pain intensity and some of the independent variables (Table 3). For example, there was a positive relationship between pain frequency and intensity and age and taking other medications.

In addition, there was a negative correlation between pain intensity and physical activity, the more strenuous the activity, the lower the intensity of the pain. There was no relationship between pain frequency and physical activity as well as between pain frequency and pain intensity, cardiovascular disease, and BMI. There were marginal negative associations between pain frequency and pain intensity and smoking (r=-0.14%, r=- 0.18%), respectively. There was also a weak but significant positive relationship between pain intensity and gender, so women reported more pain compared to men. The frequency of pain was not found to be related to gender.

The models for predicting pain frequency and pain intensity were evaluated using hierarchical regression and found significant (Tables 4 and 5). The model for predicting pain intensity was found to have a relatively significant contribution as well as marginal significance for physical activity, so that high physical activity predicts low levels of pain intensity. However, none of the individual independent variables had a distinctive unique contribution to the model. A difference in the intensity and frequency of musculoskeletal pain among patients who take different types of statin was not verified (Table 6).

Table 1. Participant characteristics

Variable	Category	Statin intake		Total	Sig.
		No	Yes		
Age (y)	M ± SD	55.3 ± 9.38	66.21 ± 9.18	59.76 ± 10.72	<.000
BMI*	M ± SD	27.3 ± 4.61	28.07 ± 6.42	27.62 ± 5.42	.371
Gender	Male, N (%)	23 (51.1)	22 (48.9)	45	.198
	Female, N (%)	74 (62.2)	45 (37.8)		
Physical Activity	No, N (%)	29 (50.9)	28 (49.1)	57	.022
	Moderate, N (%)	41 (56.2)	32 (43.8)	73	
	High, N (%)	27 (79.4)	7 (20.6)	34	
Smoking	No, N (%)	78 (58.6)	55 (41.4)	133	.787
	Yes, N (%)	19 (61.3)	12 (38.7)	31	
Cardiovascular	No, N (%)	92 (65.7)	48 (34.3)	140	<.000
	Yes, N (%)	5 (20.8)	19 (79.2)	24	

*Body Mass Index

Table 2. Musculoskeletal pain frequency and intensity and statin intake (N=164)

	Statin intake				Total	Sig.	
	No	SD	Yes	SD			
Musculoskeletal pain frequency during the last year (1-5)	3.01	.780	3.32	.610	3.14	.730	.004
Musculoskeletal pain intensity during the last week (0-10)	3.35	1.99	4.36	1.95	3.76	2.03	.001
Average number of Musculoskeletal pain sites during the last week	2.19	1.62	3.33	1.98	2.65	1.86	<.000
Average number of Musculoskeletal pain sites that disturbed work during the last three months	1.73	1.69	2.76	1.86	2.15	1.83	<.000

Table 3. Pearson correlation between musculoskeletal pain frequency and intensity and health characteristics (N=164)

	9	8	7	6	5	4	3	2	1
1. Pain frequency	-.06	.14*	.02	.23**	-.18*	.05	.20**	.64**	-
2. Pain intensity	-.16*	.21**	-.04	.25**	-.14*	.09	.25**	-	-
3. Statin intake	-.20**	.35**	.07	.50**	-.02	.32**	-	-	-
4. Cardiovascular	-.11	.39**	.11	.23**	-.02	-	-	-	-
5. Smoking	-.21**	-.03	.01	-.23**	-	-	-	-	-
6. Age	-.04	.23**	-.09	-	-	-	-	-	-
7. BMI	-.11	.01	-	-	-	-	-	-	-
8. Additional medications	-.13	-	-	-	-	-	-	-	-
9. Physical activity	-	-	-	-	-	-	-	-	-

*p < .05 **p < .01

Table 4. Multiple regression analysis for musculoskeletal pain prediction during the last year (N-164)

	B	SE	Beta	Sig.
Statin intake	.16	.14	.11	.249
Cardiovascular disease	-.12	.18	-.06	.483
Smoking	-.28	.15	-.15	.059
Age	.01	.01	.14	.136
BMI	.00	.01	.02	.776
Additional medications	.21	.23	.08	.362
Physical activity	-.06	.08	-.06	.468
R²	.09			
df	7,156			
F	2.30			< .05

Table 5. Multiple regression analysis to predict musculoskeletal pain intensity during the last week (N-164)

	B	SE	Beta	Sig.
Statin intake	.49	.38	.12	.200
Cardiovascular diseases	-.28	.48	-.05	.557
Smoking	-.70	.41	-.13	.090
Age	.02	.02	.13	.158
BMI	-.02	.03	-.05	.497
Additional medications	1.01	.63	.13	.111
Physical activity	-.43	.22	-.15	.052
R²	.13			
df	7,156			
F	3.37**			< .01

Table 6. Musculoskeletal pain frequency and intensity and statin type

	Statin type								Sig.
	Simvastatin N=20		Rosuvastatin N=18		Atorva N=28		Total N=66		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Musculoskeletal pain frequency during the last year (1-5)	3.17	.42	3.33	.51	3.44	.74	3.33	.60	.301
Musculoskeletal pain intensity during the last week (0-10)	3.84	1.62	4.14	2.00	4.93	2.07	4.38	1.96	.135
Average number of Musculoskeletal pain sites during the last week	3.65	1.84	2.78	1.59	3.46	2.30	3.33	1.99	.370
Average number of Musculoskeletal pain sites that disturbed work during the last three months	3.15	1.79	2.50	1.69	2.71	2.03	2.79	1.86	.547

Discussion

In this study, intensity and frequency of musculoskeletal pain were examined among patients who attended PT clinics, who use and do not use statins. Previous studies addressed the incidence of musculoskeletal pain in a general population with no reference to its intensity and frequency [1,2,11-14]. In addition, medication use gathered by self-report was validated by information from medical records considered to be a "gold standard" [19-21]. This information is important when assessing pain as an outcome measure in physical examination.

The similarity between the characteristics of the current study population (average age of 59.7 years and majority female) and the populations of previous studies may indicate the potential representativeness of this population [1,2]. In addition, as expected and similar to previous studies, older patients who use statins have been found to be more prone to cardiovascular disease and less physically active [1,10,28,29].

The study hypotheses were partially verified: The first hypothesis that the intensity and frequency of musculoskeletal pain are higher

among statin users has been verified. In addition, statin users have been found to report pain at more anatomical sites compared to non-statin users. This result is similar to the results of previous cross-sectional studies, which found that patients taking statins without rheumatic disease background reported a higher incidence of sites in the body with musculoskeletal pain compared to non-statin users [1,11]. However, these results are in contrast to the results of previous observational studies that showed low percentages of musculoskeletal pain reports, with no difference between statin users and non-users [12-14]. The variance of the results of those studies can be attributed to the use of different research methods and of different participant characteristics. For example, some of the studies included in literature reviews were based on creatine kinase (CK) enzyme levels and included patients who showed only high levels of the enzyme in the blood [1,11]. This information can result in underestimation of musculoskeletal pain. In addition, the population of those studies differ from patients who attend PT clinics. Some of the studies included participants from the general population [1,11] while others were hospitalized in medical institutions and therefore may present higher symptom levels [2].

For our second hypothesis, the relationship between participants characteristics and the intensity and frequency of musculoskeletal pain was verified only for the level of physical activity. The relationship between physical activity, statin use, and pain intensity has been demonstrated in the present study in several forms. First, patients taking statins are less active in comparison with patients who do not take statins. Second, a negative correlation was found between physical activity and musculoskeletal pain intensity. Finally, the level of physical activity predicted the level of pain intensity. The association between physical activity level and pain intensity was also supported in previous studies, although the populations of those studies are diverse and do not reference statins [30-33]. This finding may have clinical implications for PT. It emphasizes the need to motivate patients to be more active, integrate them into existing groups, and encourage physicians to refer this population to physical activity. Although there is a positive correlation between statin therapy and adult age, women's gender, high body mass, and taking other medications, its potency is very low.

The findings that statin therapy contributes to musculoskeletal pain should be part of the physical therapist's discretion in making patient care decisions and even coordinating prior expectations that are very important in the therapeutic arrangement. It should be noted that the statin user group, was older and had more cardiovascular disease than the non-statin group, but these variables were not related to the level of physical activity and were not predictors of the frequency and intensity of musculoskeletal pain.

As opposed to our third hypothesis, the relationship between statin type and the intensity and frequency of musculoskeletal pain was not verified. This finding differs from the results of previous literature reviews showing that the incidence of musculoskeletal pain is different among patients receiving various types of statins whereas patients receiving atorvastatin experience a higher incidence of musculoskeletal pain [12,15].

Limitations

Musculoskeletal pain is a subjective finding and, therefore, the perception of pain may vary among participants. There was no reference in the current study regarding the HMO policy regarding the choice of statin type for initiation of therapy. The HMO's guideline for physicians is to start taking simvastatin, considered a first priority before choosing atorvastatin and finally switching to rosuvastatin. So,

patients in a study taking atorvastatin or rosuvastatin have not been asked if they had previously taken simvastatin. However, the order of drug administration is not expected to affect the results of the present study. Importantly, the European Cardiology Association has no specific guideline for selecting the type of statin to start treatment and there is no preference for a specific statin type over another [7]. In the present study, as in previous studies, [12] no doses were tested, and no conclusions can be drawn about doses of statin therapy. Finally, the study was conducted in PT clinics in the Northern District of the country and included patients from the Jewish sector. This population may not represent the entire population of Israel, and especially not the Arab sector. Presumably, there are health and lifestyle differences in various geographical locations in the country.

Conclusions

In this study, the intensity and frequency of musculoskeletal pain were found to be higher among statin-users than among non-statin users patients referred to PT. In addition, statin users had higher incidence of painful sites in the body compared to non-statin users. Physical activity had a significant contribution in predicting pain intensity. These results should be considered during an assessment and treatment of patients with musculoskeletal pain who use statins. Future studies should include a nation-wide representative sample of patients.

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