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## ORIGINAL RESEARCH

# A questionnaire assessment of physical function in hyperlipidemic patients

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### Abstract

**Background:** A spectrum of myopathic manifestations has been recognized as associated with lipid lowering drug therapy (LLT), but their effect on quality of life and physical functioning is uncertain. We conducted a prospective cohort study in which physical functioning was the dependent variable, in patients with and without exposure to LLT.

**Methods:** Consecutive patients attending a risk reduction clinic were invited to participate in a questionnaire study which included demographic data, muscular symptoms, the SF-36 Physical Function Score (PF), and the modified Health Assessment Questionnaire (mHAQ). Laboratory and co-morbidity data was recorded.

**Results:** Of 117 consecutive patients invited to participate, 112 consented. Of these, 81 were receiving statins and/or fibrates as LLT and 31 were participating in a non-pharmacologic therapeutic program (NPT) of diet and exercise therapy. The mean age for the total population was 56.7 years (20-78): the LLT group 58.6 and NPT group 51.9 years. Women comprised 53% of the LLT group and 58% of the NPT. No significant differences in baseline lipid profiles, CK level, BMI, waist measurement, gender, cigarette smoking, alcohol consumption, non-steroidal anti-inflammatory drugs or acetaminophen use, frequency of myalgias, SF-36 PF or mHAQ scores were observed between groups. On comparison of gender groups, we ob-

served that men receiving LLT had significantly better SF-36 PF ( $p = 0.037$ ) than men on NPT. There were no differences in SF-36 PF or mHAQ scores between groups for females.

**Conclusion:** We found no adverse effects of LLT on physical functioning or quality of life. Indeed, men treated with LLT had significantly better SF-36 PF scores than men treated non-pharmacologically.

In the treatment of dyslipidemia/hypercholesterolemia, statins (3-hydroxy-3-methylglutaryl CoA reductase inhibitors) are widely prescribed.<sup>1</sup> There has been heightened awareness of the potential for myotoxicity with use of these agents since 2001, when cerivastatin was withdrawn from the world market.<sup>2</sup> A spectrum of myopathic manifestations in this patient population has been recognized, ranging from the extreme of fatal rhabdomyolysis to the presence of myalgias without laboratory abnormalities.<sup>3-6</sup> Myopathic complications have also been reported with use of fibrates.<sup>7</sup>

Concerns have been raised as to the potential deleterious effect of lipid lowering therapy on physical

function, particularly in the elderly population.<sup>8</sup> Conversely, it has been recognized that health-related quality of life, associated with physical function, is decreased in patients with common cardiometabolic risk factors including hyperlipidemia.<sup>9</sup> Major clinical trials have noted the high frequency of musculoskeletal complaints,<sup>10,11</sup> but no trial has looked at the effect of such complaints on physical functioning.

In this study we employed the SF-36 Physical Function Score (PF)<sup>12</sup> and the modified Health Assessment Questionnaire (mHAQ)<sup>13</sup> to evaluate physical functional status in a hyperlipidemia clinic patient population and compare those treated with lipid lowering pharmacotherapeutics to those on non-pharmacological regimens.

## Methods

This study was approved by, and carried out according to, the instructions of the University of Saskatchewan ethics committee. This was a prospective cohort study of patients attending the Cardiovascular Risk Factor Reduction clinic at Royal University Hospital over a three month period.<sup>14</sup> This population consisted of both pharmacotherapeutically-treated patients and those on a non-pharmacotherapeutic treatment program. Individual patient treatment was based on physician and patient preference rather than any specific criteria. One hundred and seventeen consecutive patients were invited to participate in this study. One hundred and twelve agreed to participate. Our inclusion criteria included a history of dyslipidemia coupled with either use of a lipid lowering pharmacotherapeutic agent or non-pharmacologic therapeutic program. All patients had been counseled concerning the value of appropriate diet and exercise regimens. Informed consent was obtained prior to administration of the questionnaire. Participants' medical records were reviewed.

The questionnaire included demographic data, the SF-36 PF (potential score range 0-100) [12], and the mHAQ (potential score range 0-24).<sup>13</sup> The mHAQ is

scored such that the greater the numerical score, the greater the functional incapacity, whereas for the SF-36 PF score the converse is true: the lower the score the greater the functional incapacity. Directed questions on the presence of musculoskeletal discomfort, knowledge of previous diagnoses of myositis, fibromyalgia, or previous findings of elevated creatine kinase (CK) or muscle weakness were also included.

## Statistical Analysis

The primary outcome measure evaluated in this study was the SF-36 PF score, whereas the independent variable was LLT. We chose a standard two-sided significance level of 0.05, power of 0.80, and employed published standard deviation data in our sample size estimation.<sup>15</sup> We identified a 15% difference in the mean SF-36 PF score as a minimal clinically significant effect size. Pre-screening of clinic charts permitted identification of an unequal allocation ratio (2.5) between treatment groups. Our minimum sample size calculation required 28 subjects in the non-pharmacologically treated group and 70 subjects in the lipid lowering therapy group for a total of 98 subjects in all.<sup>16</sup>

The statistical software package SPSS v.12.0 was employed for data entry and analysis. Between-group comparisons were performed using independent t-tests for continuous data and chi-square analysis of categorical data. The SF Health Outcomes™ Scoring Software was employed to determine SF-36 PF scores.

## Results

Of the 117 consecutive patients approached to participate in this study, 112 consented and completed the questionnaire. Of these, 81 were treated pharmacologically, with 64 receiving statin monotherapy, 12 receiving fibrate monotherapy and 5 receiving combination therapy. For 31 patients, diet and exercise therapy were recommended, without additional pharmacotherapy. For the purposes of data analysis, the total

population was divided into two groups: the pharmacologic treatment group receiving lipid lowering therapy (LLT) and the non-pharmacologic treatment (NPT) group. No significant differences were observed between these two groups in pretreatment laboratory parameters (total cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), triglyceride, creatine kinase (CK) levels), cigarette smoking, alcohol consumption or use of non-steroidal anti-inflammatory drugs or acetaminophen. Current laboratory parameters demonstrated a significantly lower LDL level in the pharmacologically treated group ( $-0.49$  mmol/L; 95% C.I.  $-1.173$ ,  $-0.189$ ,  $p = 0.007$ ). The overall mean age for the population was 56.7 (20-78) years. The LLT group were older: 58.6 (22-78) versus 51.9 (20-74) years ( $p = 0.007$ ). There was no significant difference in gender distribution between groups. The LLT group included 43 women (53.1%), and the NPT group 18 women (58.1%). The average Body Mass Index (BMI) of the total population was  $32.8$  kg/m<sup>2</sup> (SD 7.96) with no significant differences found between patient groups. The female subjects receiving lipid lowering therapy were more likely to be older (mean age  $59.3 \pm 11.38$  years) in comparison with women on non-pharmacologic therapy (mean age  $49.9 \pm 15.0$  years;  $p = 0.010$ , 95% C.I.: 2.354, 16.426). Women receiving lipid lowering therapy were also more likely to have hypertension, diabetes, or coronary artery disease than women on non-pharmacologic therapy. No differences in these cardiovascular risk factors or in age were seen in the men, based on treatment group.

Information on the presence of musculoskeletal related co-morbidities was collected, and is summarized in Table 1. No significant differences in musculoskeletal symptomatology or self-reported abnormalities (Table 2) were noted between groups.

Two measures of physical functioning were used: the SF-36 PF and the mHAQ. Mean scores are recorded in Table 3. No significant differences were observed between treatment groups in either of these measures; however, there was a correlation between sex and LLT for SF-36PF scores: men on LLT scored higher than those on NPT ( $48.40 \pm 9.75$  vs.  $41.82 \pm 8.62$ ,  $p = 0.037$ ).

## Discussion

We found no effect of LLT on physical functioning, despite a fairly high prevalence (20-40%) of musculoskeletal complaints. Although this is an observational study, our groups were well balanced for previous musculoskeletal complaints that could affect physical functioning. Furthermore, our LLT group was slightly but significantly older, a variable that may impede physical functioning. Surprisingly, we found that men on LLT actually had higher physical functioning on the SF-36PF and a trend towards the same on the mHAQ. Given that this is a subgroup of an observational study, this finding must be interpreted with caution.

It is unclear why men receiving lipid lowering therapy would have better physical functioning scores than men on diet and exercise alone. It could potentially relate to a greater commitment on the patient's

TABLE 1: Co-morbidities of study population

	Total population	LLT group (n=81)	NPT group (n=31)
Diabetes mellitus	52 (46.4%)	42 (51.9%)	10 (32.2%)
Hypothyroid	14 (12.5%)	8 (9.9%)	6 (19.4%)
Rheumatoid Arthritis	11 (9.8%)	11 (13.5%)*	0*
Osteoarthritis	36 (32.1%)	23 (28.4%)	13 (41.9%)
Fibromyalgia	8 (0.9%)	5 (6.2%)	3 (9.7%)
Tendonitis	15 (13.4%)	10 (12.3%)	5 (16.1%)

\* between group comparison  $p = 0.031$

TABLE 2. Musculoskeletal symptomatology in the population treatment groups

	Total population	LLT group (n=81)	NPT group (n=31)
Previous myositis*	2 (1.8%)	2 (2.5%)	0
Previous elevated CK*	4 (3.6%)	3 (3.7%)	1 (3.2%)
Muscle weakness*	46 (41.1%)	37 (45.7%)	9 (29%)
Diffuse MSK discomfort*	22 (19.6%)	17 (21.0%)	5 (16.1%)

Population percentages in brackets, \* self-reported

TABLE 3: Physical Functioning Scores in Population Treatment Groups

	Total population (n = 112)	LLT group (n = 81)	NPT group (n = 31)	Significance (p value)	95% C.I.
Mean mHAQ score	0.928 (1.542)	0.875 (1.594)	1.065 (1.413)	0.564	-.0884, 0.459
Mean SF-36 PF score	45.57 (10.30)	45.73 (10.82)	45.17 (9.05)	0.800	-3.806, 4.923
in Men	46.65 (9.82)	48.40 (9.75)	41.82 (8.62)	0.037	0.4111, 12.747
in Women	44.67 (10.68)	43.38 (11.28)	47.59 (8.79)	0.166	-10.205, 1.793

Standard deviations in brackets, C.I.: Confidence Intervals

part to cardiovascular risk reduction with diligent attention to diet and exercise; however, the BMI and waist circumference were not significantly different between groups. It is also interesting that women did not exhibit such a difference between groups. The female subjects receiving lipid-lowering therapy also were observed to be more likely to have significant cardiovascular risk factors including diabetes, hypertension, known coronary artery disease, and, unlike the men, tended to be older than those who were on non-pharmacologic therapy. This age difference may contribute to physical function score differences based on gender. Another intriguing possibility relates to recently recognized anti-inflammatory action of statins that may influence a patient's physical functional capacity.<sup>17,18</sup>

Limitations of our study include the relatively small sample size. This results in decreased ability to detect smaller differences between treatment groups. This study was powered to detect a 15% difference in the SF-36 PF scores between pharmacologic and non-pharmacologic treatment groups. Although smaller differences may be overlooked, we feel this provides us with a clinically useful perspective on physical functional capacity. The heterogeneity of the treatment population is an additional potential concern, as it has been recognized that different statins, as well as dif-

ferent fibrates have been associated with some variability in risk of myotoxicity.<sup>4,19</sup> Combination therapy has been recognized to potentially further increase this risk.<sup>19,20</sup> Whether or not these differences would extend to milder degrees of muscle involvement is unknown. Moreover, in contrast to controlled clinical trials, most outpatient clinic populations will demonstrate similar heterogeneity. We feel our study population reflects that seen in many outpatient clinic settings.

## Conclusions

Although musculoskeletal complaints were common in this 'real world' group of patients taking LLT, there was no adverse effects on their physical functioning or quality of life. We can reassure prescribers that most patients will accept minor 'adverse effects' and reap the benefit from LLT.

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