ORIGINAL ARTICLE

Effect of long-term physical activity on PCSK9, high- and low-density lipoprotein cholesterol, and lipoprotein(a) levels: a prospective observational trial

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KEY WORDS

high-density lipoprotein, lipoprotein(a), low-density lipoprotein, physical activity, proprotein convertase subtilisin/kexin type 9

ABSTRACT

INTRODUCTION Since proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were introduced to the market, the interest in PCSK9 metabolism has increased dramatically.

OBJECTIVES We investigated prospectively the influence of long-term physical activity on PCSK9, high- and low-density lipoprotein cholesterol (HDL-C and LDL-C, respectively), and lipoprotein(a) levels [Lp(a)].

PATIENTS AND METHODS A total of 109 participants were recruited and instructed to increase their sport pensum by 75 min/wk of vigorous-intensity or 150 min/wk of moderate-intensity endurance training (or a mixture) within the calculated training pulse for 8 months. Stress tests were performed at baseline and at the end of the study to prove and quantify the performance gain. PCSK9 levels were measured at baseline and after 2, 6, and 8 months by an enzyme-linked immunosorbent assay. HDL-C, LDL-C, and Lp(a) levels were measured at baseline and every 2 months.

RESULTS The final study sample included 79 subjects, who showed a mean performance gain of 11.4%. Mean (SD) PCSK9 and HDL-C levels increased significantly from 224.7 (66.8) ng/ml to 243.4 (84.0) ng/ml ($P = 0.04$) and 58.3 (18.4) mg/dl to 61.1 (18.5) mg/dl ($P = 0.014$), respectively. Mean (SD) LDL-C levels decreased significantly from 115.0 (33.4) mg/dl to 109.8 (31.7) mg/dl ($P = 0.04$), but there was no significant change in mean (SD) Lp(a) levels: 37.9 (51.9) nmol/l to 43.3 (60.6) nmol/l; $P = 0.218$.

CONCLUSIONS Our study showed a decrease in LDL-C levels induced by a long-term physical activity with a simultaneous increase in PCSK9 levels. PCSK9 is essential in lipid metabolism and should not be basically considered as harmful. It is possible that a certain amount of PCSK9 is beneficial to ensure an adequate lipid supply.

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INTRODUCTION Physical activity has been shown to have a protective effect on risk factors and pathomechanisms causing or being involved in the development of cardiovascular disease (CVD), reflected by activity-induced modification of biomarkers such as interleukin 6 (IL-6), high-sensitivity C-reactive protein (CRP), endocan, and cathepsin S (for inflammation)[1,2] or endostatin (for angiogenesis).[3] The lipid metabolism plays an important role in CVD, particularly since proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (eg, evolocumab, alirocumab; both monoclonal antibodies) were introduced to the market. The first study connecting PCSK9 with the lipid metabolism was done by Abifadel et al,[4] while investigating autosomal dominant hypercholesterolemia. PCSK9 is an important regulator of low-density lipoprotein cholesterol (LDL-C)

metabolism. In the absence of PCSK9, circulating LDL-C binds to the low-density lipoprotein (LDL)-receptor of liver cells, and the complex gets incorporated. Owing to the low pH value in the endosomes, the LDL-receptor/LDL-C complex separates: LDL-C is metabolized and the LDL-receptor returns to the cell surface. PCSK9 inhibitors were shown to lower not only LDL-C levels (by 40%–72% together with atorvastatin)[5] but also lipoprotein(a) levels [Lp(a)] (up to 31%).[6] As physical activity has been shown to beneficially modify lipid metabolism, we aimed to investigate the effect of long-term physical activity on serum PCSK9 as well as LDL-C, Lp(a), and HDL-C levels.

PATIENTS AND METHODS In total, 109 participants were recruited. The inclusion criteria were as follows: age between 30 and 65 years, 1 or more classic cardiovascular risk factors as described below, and the physical ability to perform endurance exercise. The exclusion criteria were age below 30 years or above 65 years, no ability to perform endurance exercise, current oncologic or infectious disease (increased inflammatory parameters at baseline and/or medical history data). Of the 109 participants, 98 completed the study, while 11 were lost to follow-up for different reasons (eg, accidents, loss of motivation). However, 19 participants showed no performance gain (determined by bicycle stress tests) and were therefore excluded. Baseline data of the excluded participants are presented in Supplementary material online. The final study sample consisted of 79 participants aged 30 to 65 years with at least 1 classic cardiovascular risk factor defined as follows: overweight (body mass index >25.0 kg/m^2), hypertension (defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >85 mmHg at rest or the use of antihypertensive medication), hyperlipidemia or dyslipidemia (history of statin therapy), type 2 diabetes (defined as glycated hemoglobin A_{1c} exceeding 6.5% or the use of diabetes medication), current smoking, known coronary heart disease (history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or stroke), and a positive family history of myocardial infarction, CVD, or stroke in a mother or father. The weekly alcohol intake was measured in units: 1 unit corresponded to 0.33 l of beer, 0.125 l of red/white wine, or 0.02 l of spirits.

The study was carried out in accordance with the Declaration of Helsinki and its later amendments as well as with the ethical standards in sports and exercise research.[7] The protocol was approved by the Ethical Commission of the Medical University of Vienna, Austria (EC-number: 1830/2013), and informed consent was obtained from all participants before inclusion.

Measurement of anthropometric data, training diary, and bicycle stress test (ergometry) After detailed medical history and physical examination including the measurement of height, weight, body water, body muscle mass, and body fat (with a diagnostic scale, Beurer BG 16, Beurer GmbH, Ulm, Germany), participants were asked to perform a bicycle stress test (ergometry) at baseline to define their performance level and to calculate their individual training pulse/target heart rate (using the Karvonen formula with an intensity level of 65% to 75% for moderate and 76% to 93% for vigorous intensity). Participants were allowed to decide the type of physical activity/sports; however, they were asked to perform at least 75 min/wk of vigorous- or 150 min/wk of moderate-intensity endurance training (or a mixture; strength training was allowed but not mandatory) within the calculated training pulse. The second bicycle stress test was performed at the end of the study (after 8 months) to prove and quantify exactly and objectively the performance gain. The bicycle stress tests were always monitored by an electrocardiogram and performed with the same system (Ergometer eBike comfort, GE Medical Systems, Freiburg, Germany) starting with 25 watts and increasing every 2 minutes by 25 watts (according to the protocol of the Austrian Society of Cardiology, which is equivalent with the guidelines of the European Society of Cardiology). Blood pressure and heart rate were measured every 2 minutes. Participants were told to cycle with 50 to 70 revolutions/min until exhaustion. The target performance was calculated using body surface (calculated according to the DuBois formula: body surface [m^2] = 0.007184 × height [cm] $^{0.725}$ × weight [kg] $^{0.425}$),[8] sex, and age. An individual target performance of 100% represents the performance of an untrained collective. Concerning nutrition, participants were asked not to change their eating habits. They also received a training diary to record their training effort during the study period.

Laboratory analysis Blood samples were drawn not in the fasting state. Blood samples for the determination of PCSK9 were taken at baseline and at 2, 6, and 8 months. PCSK9 levels were assessed according to the manufacturer's instructions. We used the Human Proprotein Convertase 9/PCSK9 Quantikine ELISA kit, which recognizes free and LDL–receptor-bound PCSK9 (R&D Systems, Abingdon, United Kingdom). All other samples were taken at baseline and every 2 months. LDL-C and HDL-C levels were assessed in a routine laboratory analysis using a homogeneous enzymatic (colorimetric) assay. All blood samples were taken from an arm vein, after 10 minutes of lying still, and with a tube/adapter system. Samples for the determination of routine laboratory parameters were analyzed immediately after drawing.

Statistical analysis A statistical analysis was done using SPSS 20.0 (IBM SPSS Statistics, New York, United States). Continuous and normally distributed data were presented as mean (SD). Nonnormally distributed data were presented by median

TABLE 1 Risk factor profile and anthropometric and routine laboratory parameters at baseline

Parameter	Value
Hypertension, n (%)	26 (33.8)
Dyslipidemia, n (%)	22 (28.6)
Type 2 diabetes, n (%)	1 (1.3)
Overweight, n (%)	50 (65.0)
Previous smoking, n (%)	32 (41.6)
Smoking, n (%)	15 (19.5)
Known CHD/stroke, n (%)	16 (20.8)
Positive family history, n (%)	31 (40.3)
Alcohol, units/wk	3.0 (3.8)
Age, y	48.8 (7.0)
BMI, kg/m^2	27.5 (4.2)
Body water, %	52.4 (5.8)
Body fat, %	29.5 (9.8)
Body muscle, %	35.0 (4.1)
SBP, mm Hg	142.8 (14.4)
DBP, mm Hg	77.8 (7.7)
Performance at baseline, %	103.9 (18.6)
Performance at 8 months, %	115.3 (19.1)
Performance gain, %	11.4 (6.6)
Moderate intensity, min/month	1255 (913)
Vigorous intensity, min/months	295 (342)
Erythrocytes, T/l	4.7 (0.4)
Hemoglobin, g/dl	14.1 (1.4)
Hematocrit, %	40.4 (3.4)
Thrombocytes, G/l	241.7 (51.5)
Leukocytes, G/l	6.5 (1.6)
Sodium, mmol/l	141.4 (1.7)
Potassium, mmol/l	4.2 (0.3)
Chloride, mmol/l	101.1 (2.0)
Calcium, mmol/l	2.3 (0.1)
Phosphate, mmol/l	1.1 (0.1)
Magnesium, mmol/l	0.8 (0.1)
Creatinine, mg/dl	0.9 (0.2)
BUN, mg/dl	16.2 (16.1)
Uric acid, md/dl	5.3 (1.5)
Lipase, U/l	40.4 (17.0)
Cholinesterase, kU/l	8.2 (1.7)
Alcaline phosphatase, U/l	62.9 (40.0)
GOT, U/l	25.3 (7.8)
GPT, U/l	27.1 (12.1)
GGT, U/l	30.4 (47.0)
LDH, U/l	173.6 (26.3)

Data are presented as mean (SD) unless otherwise indicated.

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CHD, coronary heart disease; DBP, diastolic blood pressure; GOT, glutamat-oxalacetat-transaminase; GGT, gamma-glutamyl transferase; GPT, glutamat-pyruvat-transaminase; LDH, lactate dehydrogenase; SBP, systolic blood pressure

(interquartile range). Single correlations involving only 2 normally distributed variables were calculated using the Pearson correlation coefficient, and single correlations involving 2 nonparametric and/or ordinal variables were calculated using the Spearman's rho analysis. A backwards multiple linear regression analysis was performed to investigate the association of covariables that correlated significantly with baseline PCSK9 levels. To investigate the difference between the levels at baseline and those at 8 months, we used a parametric test for 2 related samples (paired-sample *t* test). All tests were performed in accordance with 2-sided testing, and a *P* value of 0.05 or less was considered significant.

RESULTS Baseline medical history, anthropometric, and laboratory parameters are shown in TABLE 1. The study population consisted of 79 participants (29 women, 50 men) with a mean (SD) age of 48.8 (7.0) years. The most prevalent CVD risk factors were overweight (65%), previous and current smoking (42% and 20%, respectively), and a positive family history of CVD (40%) and hypertension (34%). The mean (SD) training effort according to the training diaries was 1255 (913) min/months of moderate-intensity and 295 (342) min/months of vigorous-intensity training. The mean (SD) performance gain after 8 months measured by bicycle stress tests was 11.4% (6.6%). The mean (SD) alcohol intake per week was 3.0 (3.8) units. All anthropometric and laboratory data were within the normal ranges.

At baseline, PCSK9 levels correlated positively with age (P = 0.014; r = 0.247), weekly alcohol intake (P value = 0.006; r = 0.281), and the levels of potassium (P = 0.008; r = 0.269), calcium (P = 0.019; r = 0.237), blood urea nitrogen (P = 0.005; r = 0.284), cholinesterase (P = 0.046; r = 0.203), total cholesterol (P = 0.024; r = 0.230), apolipoprotein B (P = 0.009; r = 0.265), glycated hemoglobin A_{1c} (P = 0.008; r = 0.269), and IL-6 (P = 0.029; r = 0.222). However, none of these parameters remained significant in the backwards multiple linear regression analysis.

During the 8-month follow-up, PCSK9 and HDL-C levels increased with an increased physical activity pensum from a mean (SD) of 224.7 (66.8) ng/ml to 243.4 (84.0) ng/ml (P = 0.04) and a mean (SD) of 58.3 (18.4) mg/dl to 61.1 (18.5) mg/dl (P = 0.014), respectively. Mean (SD) LDL-C levels decreased from 115.0 (33.4) mg/dl to 109.8 (31.7) mg/dl (P = 0.040), but there was no significant change in Lp(a) levels (mean [SD], 37.9 [51.9] nmol/l to 43.3 [60.6] nmol/l; P = 0.218) (FIGURE 1). There was no correlation between the percentage performance gain and the increase in PCSK9 levels (P = 0.698) or the decrease in LDL-C levels (P = 0.591).

We observed differences between baseline and endpoint values for the following parameters: body water (52.4% vs 54.3%; P <0.001), body fat (29.5% vs 26.3%; P = 0.001), systolic blood pressure (142.8 mm Hg vs 138.9 mm Hg; P = 0.050),

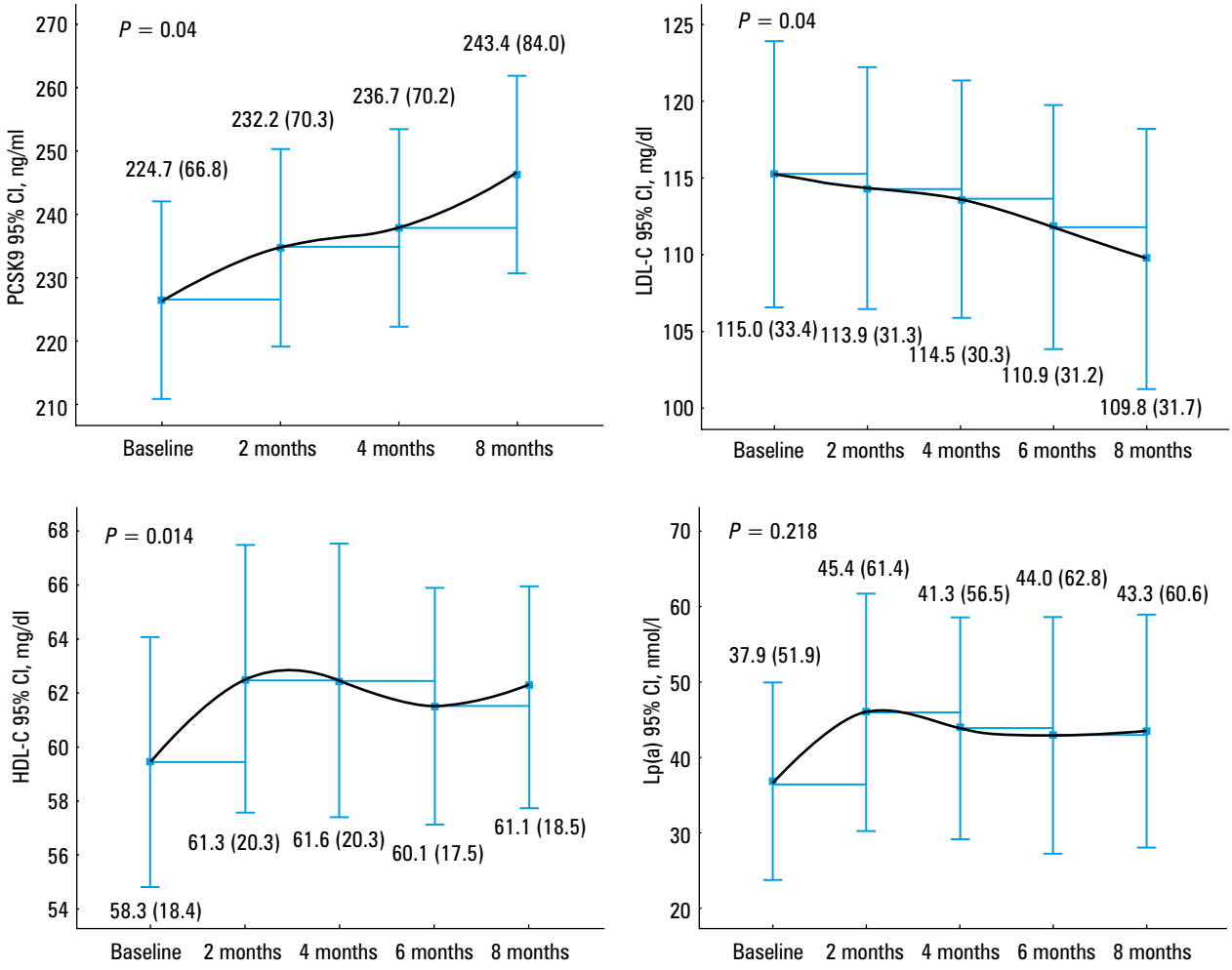

FIGURE 1 Changes in proprotein convertase subtilisin/kexin type 9 (PCSK9), high- and low-density lipoprotein cholesterol (HDL-C and LDL-C), and liporotein(a) [Lp(a)] levels during the 8-month follow-up; a *P* value calculated with the paired-sample *t* test (baseline/endpoint levels); data presented as mean (SD)

apolipoprotein A1 (155.4 mg/dl vs 164.4 mg/dl; $P < 0.001$), apolipoprotein B (101.3 vs 97.7 mg/dl; $P = 0.035$), and interleukin 6 (2.6 vs 2.0 pg/ml; $P = 0.006$).

DISCUSSION Our study showed a significant activity-induced increase in PCSK9 levels with a simultaneous significant decrease in LDL-C levels in a cohort of 79 participants with a proven and quantified performance gain within 8 months of training. An activity-induced decrease in LDL-C levels (and also an increase in HDL-C levels) is well known and has been shown before; however, the increase in PCSK9 levels was unexpected, in particular with simultaneously decreasing LDL levels. To interpret these results, we have to elaborate on the PCSK9 and LDL-C metabolism.

The inactive PCSK9 is mainly produced in liver cells and is secreted into circulation after autocatalytic cleavage in the endoplasmatic reticulum. The clinical relevance of PCSK9 is accounted for by its ability to bind to the LDL-receptors. The LDL-receptor/PCSK9 complex is incorporated and the LDL-receptor degraded, and, consequently, it is not available for further LDL-C binding. As a result, less LDL-C is incorporated and metabolized by the liver cells, and the LDL-C levels increase.[9]

PCSK9 has already been investigated as a therapeutic target. PCSK9 inhibitors (evolocumab, alirocumab) bind to the circulating PCSK9 and thus inhibit the degradation of the LDL-receptor. These 2 monoclonal antibody inhibitors of PCSK9 have been approved for treatment of elevated LDL-C levels in patients who have not sufficiently responded to statin treatment or do not tolerate statins well.[10] The reason for the PCSK9–inhibitor-induced reduction in Lp(a) levels is not completely understood because Lp(a) has not been previously considered to be involved to any significant extent in the metabolization of the LDL-receptor.[11] However, in vitro studies showed that PCSK9 was indeed able to modulate Lp(a) internalization via the LDL-receptor.[12] Although the molecular mechanisms of the PCSK9 inhibitors such as alirocumab and evolocumab still need to be elucidated, both showed that treatment was associated with a significant reduction in the rate of CVD events.[13,14] The PCSK9 inhibitors lead to a considerable reduction in LDL-C levels (39% to 62% for alirocumab and 47% to 56% for evolocumab); however, LDL-C levels were shown to drop below 25 mg/dl with possible gastrointestinal, metabolic, and neurocognitive adverse effects in approximately 37% of patients receiving evolocumab and 24% of patients receiving alirocumab.[15]

Circumstances that influence the expression or secretion of PCSK9 are mostly unknown; however,

statins have been shown to upregulate the PCSK9 expression in the liver.[16] Physical activity is well known to have a beneficial effect on the lipid profile by increasing HDL-C and decreasing triglyceride levels. Although data on the effect of physical activity on PCSK9 levels are limited, it has been shown previously that daily physical activity at the work place (using stairs instead of elevators) is independently associated with a decrease in serum PCSK9 levels in healthy individuals. Although this study by Kamani et al[17] is of great interest because it was the first clinical trial investigating the influence of physical activity on PCSK9 levels, data were obtained from a small population without a control group and the maximum oxygen consumption was measured by the Chester Step Test instead of bicycle stress tests. Moreover, we cannot confirm these results. In our cohort of individuals with proven performance gain, PCSK9 levels increased continuously during the follow-up. Although PCSK9 levels increased, we observed continuously decreasing LDL-C levels.

PCSK9 acts by reducing the amount of the LDL-receptor at the cell surface of liver cells. Thus, high PCSK9 levels are typically accompanied by high LDL-C levels. Therefore, the discrimination of PCSK9 and LDL-C is of special interest and suggests that regular physical activity leads to a decrease in circulating LDL-C levels independently from (increasing) PCSK9 levels. PCSK9 is essential in lipid metabolism and should not be basically considered as harmful. It is entirely possible that a certain amount of PCSK9 is beneficial, for example, in the setting of increased metabolism (eg, sports activity with moderate intensity as was the case in our participants) to ensure an adequate supply of lipids. Probably, as already described, long-term physical activity leads to a decrease in LDL-C levels, and due to the lower LDL-C amount, less PCSK9 is used up and therefore serum PCSK9 levels increase. Another possible explanation concerns inflammation: it has been shown that acute physical strain increases inflammatory parameters, such as IL-6 and CRP. In particular, CRP levels are increased even 48 hours after a prolonged physical strain.[18] A subsequent study demonstrated that inflammation (caused by infection) stimulates the expression of PCSK9.[19] Thus, it might be possible that immune effects of physical activity (eg, an increase in CRP or IL-6 levels) influence PCSK9 levels. However, because of the lack of biochemical or molecular analysis, these are speculative approaches and need to be investigated in further research. In particular, the effect of sports in patients with (familial) hyper- or dyslipidemia in addition to PSCK-9-inhibitor intake needs to be addressed.

Limitations First, although it was a prospective study, the number of participants was relatively low and there was no control group. Second, there might have been uncontrolled factors (eg, lipid uptake/nutrition) affecting PCSK9, HDL-C, LDL-C, and Lp(a) levels. Third, due to the low number of female participants, a sex-specific analysis was not possible. Fourth, although changes in PCSK9 levels during the follow-up were statistically significant, they were relatively small and probably not clinically relevant.

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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Contribution statement MS contributed to study design, clinical investigation, performing bicycle stress tests/follow-up, statistical analysis, manuscript preparation, and final approval of the manuscript. I-AC and DD contributed to clinical investigation and performing bicycle stress tests/follow-up. ME contributed to study design, statistical analysis, and final approval of the manuscript. MF-S contributed to data acquisition and laboratory analysis. BL contributed to statistical analysis and final approval of the manuscript. JB-K contributed to manuscript preparation, performing bicycle stress tests, and final approval of the manuscript. SG contributed to clinical investigation, performing bicycle stress tests/follow-up, and final approval of the manuscript. JS-J contributed to study design, manuscript preparation, and final approval of the manuscript.

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