Decreased Skeletal Muscle Capillary Density Is Related to Higher Serum Levels of Low-Density Lipoprotein Cholesterol and Apolipoprotein B in Men

Naoko Shono, Masao Mizuno, Hirofumi Nishida, Yasuki Higaki, Hidenori Urata, Hiroaki Tanaka, Bjørn Quistorff, Bengt Saltin, Munehiro Shindo, and Masahiro Nishizumi

The relationships between skeletal muscle morphology, particularly muscle fiber capillary density, and serum lipid profiles were evaluated in 25 non-obese men aged 18 to 36 years (body mass index [BMI], 22.7 ± 2.5 kg/m^2; body fat, 13.6% ± 4.0%, maximal oxygen uptake [$\dot{V}O_2$max], 46.2 ± 6.3 mL/kg/min). Skeletal muscle samples were taken from the vastus lateralis using the needle-biopsy method. The fiber types (I, IIa, and IIx) and their percent distribution, the indices of capillary density, and the diffusion index expressed as the cross-sectional area occupied by one capillary were determined. Blood samples were drawn from the antecubital vein after a 12-hour fast. Based on Pearson's correlation analysis, the number of capillaries around type IIx fiber correlated inversely with the serum level of low-density lipoprotein cholesterol ([LDL-C] $r = -.50$, $P < .05$). The number of capillaries per fiber (cap/fiber ratio), number of capillaries per area (cap/mm^2), and capillaries around each fiber type correlated inversely with the serum level of apolipoprotein B ([apo B] $r = -.40$ to $-.54$, $P < .05$ to .01). Further, the diffusion index for each fiber type correlated positively with LDL-C and apo B ($r = .42$ to .50, $P < .05$ to .01). Among 14 subjects in whom high-density lipoprotein cholesterol (HDL-C) subfractions were analyzed, a positive correlation was found between cap/mm^2 and HDL2-C ($r = .64$, $P < .05$). Partial correlation analysis showed that these correlations either remain or improve after adjusting for age, $\dot{V}O_2$max, and body fatness. These results indicate that skeletal muscle capillary density and diffusion capacity are related to lipid and apolipoprotein concentrations for both type I and type II fibers.

THE SKELETAL MUSCLE characteristics have been suggested to be closely related to several pathological conditions in studies focusing on the specific role of the muscle fiber type.[1] There is a wide variability of muscle fiber types in slow-twitch ([ST] type I) and fast-twitch (type IIa and type IIx) muscles in humans. An increase in type II fibers, particularly type IIx, and/or a decrease in type I fibers have been found in individuals with obesity,[2] hypertension,[3] insulin resistance,[4] and coronary heart disease (CHD).[5] These reports suggest that the muscle fiber type may be a predisposing factor for these risk factors or resultant diseases.

However, there is another possibility that the metabolic and vascular properties of the muscle may be related to these conditions. Low capillary density was observed to be characteristic of patients with essential hypertension,[6] obesity,[4,7] and diabetes mellitus.[8] In addition, several lines of evidence have demonstrated that the capillary density and oxidative capacity appear to be more strongly correlated with insulin sensitivity[2,4] and body fatness[7] than the prevalence of a specific fiber type.

Only a few reports have been published on the relationships between muscle fiber characteristics and serum lipids. Tikkanen et al[5] found significant differences in both serum lipids and the percentage of ST (type I) fibers in sedentary men, joggers, and patients with CHD. They also demonstrated that the percentage of type I fibers independently correlates with serum high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (apo) A-1 levels even after considering the confounding factors. They hypothesized that type I fibers have a high capacity to metabolize fatty acids liberated by lipoprotein lipase (LPL) from triglyceride (TG)-rich lipoprotein, which in turn elevates serum HDL-C levels. Their speculation was based on the fact that type I fibers have a generally high number of capillaries,[9] and the activity of skeletal muscle LPL correlates with the percentage of type I fibers[10] and also with the capillary density.[11] However, it has not been demonstrated as to whether muscle fiber capillary density influences serum lipid levels as well. In the present study, we thus investigated the leg muscle fiber morphology in healthy men with a wide range of serum lipid profiles.

SUBJECTS AND METHODS

Subjects

Twenty-five healthy Japanese men with a mean age of 23.7 years volunteered for the study. The study design was approved by the ethics committee of Fukuoka University, and oral and written informed consent was obtained from each subject. The subjects were not involved in athletic sports, but they participated in various kinds of recreational physical activities. Twelve subjects occasionally consumed a light to moderate amount of alcohol. Six subjects smoked 10 to 20 cigarettes per day. All were free of any detectable cardiovascular, metabolic, and musculoskeletal diseases.

Muscle Biopsies

Muscle biopsies were obtained under local anesthesia from the middle lateral portion of the left vastus lateralis using the needle-biopsy technique.[12] The muscle sample was immediately mounted in an embedding medium (OCT compound; Miels Tissue Tek, CA), frozen in isopentane cooled with liquid nitrogen, and stored at −80°C until analysis. Serial 10-μm cross-sections were cut using a cryostat at −20°C and incubated for myofibrillar adenosine triphosphatase reaction at pH 9.4.[13] To identify different fiber types, the sections were preincubated at pH 4.3, 4.6, and 10.3.[14] More than 200 fibers were counted for each subject, and the cross-sectional area was calculated. Fiber type was expressed as the percent distribution area of the fiber type (types I, IIa, and IIx). Recently, the primarily denoted type IIb fibers in human skeletal muscle have been shown to resemble type IIx

From the Department of Community Health Science, Saga Medical School, Saga, Japan; Copenhagen Muscle Research Center, Copenhagen, Denmark; and Faculty of Sport and Health Science, Department of Internal Medicine, Fukuoka University, Fukuoka, Japan.

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Address reprint requests to Naoko Shono, MD, Department of Community Health Science, Saga Medical School, Nabeshima 5-1-1, Saga 849-8501, Japan.

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fibers in rat muscle. Rat type IIb fibers have not been found in humans.[15] Amylase–periodic acid–Schiff staining was used to visualize the capillaries.[16] Capillary density was expressed as (1) the number of capillaries per fiber (cap/fiber ratio), (2) the number of capillaries per area (cap/mm^2), (3) the number of capillaries around each fiber type, and (4) the cross-sectional area occupied by one capillary (diffusion index). All of these values were calculated using COMFAS (Scan Beam, Hadsund, Denmark).

Anthropometric Measures

Height was measured to the nearest centimeter, and weight was measured (with subjects in their underwear) to the nearest 0.1 kg. The body mass index (BMI) was calculated as the ratio of body weight in kilograms to height in meters squared. Percent body fat was calculated based on the triceps and subscapular skinfold thickness measured using a Harpenden caliper by the Brozek-Henschel formula[17] after estimating body density according to the method of Nagamine and Suzuki.[18] The waist circumference was measured at the level of the umbilicus and hip circumference was measured over the widest part of the hip region to calculate the waist to hip ratio (WHR).

Metabolic Measures in Blood

Blood samples were drawn from the antecubital vein after a 12-hour fast. The serum samples were stored at −80°C for subsequent analysis of the following variables: total cholesterol (TC), HDL-C, TG, apo A-1, apo B, glucose, immunoreactive insulin (IRI), and C-peptide. TC, HDL-C, and TG were analyzed by enzymatic methods. Apolipoprotein levels were measured using a turbidimetric immunoassay. The HDL3-C level was measured after precipitation of HDL2-C with dextran sulfate, and HDL2-C was calculated as the difference between HDL-C and HDL3-C. The IRI level was measured by a radioimmunoassay technique using IRI kits (Pharmacia, Uppsala, Sweden). The C-peptide level was measured by a solid-phase radioimmunoassay method using C-peptide RIA Shionogi II kits (Osaka, Japan). The intraassay and interassay coefficients of variation were less than 7.3% and 8.1%, respectively. Low-density lipoprotein cholesterol (LDL-C) was calculated using the method of Friedwald et al.[19]

Physiological Measures

Maximal oxygen uptake ($\dot{V}O_2$max) was measured using an electrically braked cycle ergometer (Load Excalibur, Groningen, The Netherlands) based on the leveling-off criteria. The workload was initially set at 10 W and then increased by 15 W/min. $\dot{V}O_2$ was measured continuously using the breath-by-breath method (RM-300; Minato, Osaka, Japan), and both the O_2 and CO_2 fractions were analyzed by a mass spectrometer (model 1100; Perkin-Elmer, Norwalk, CT).

Statistical Analysis

Because of a skewed distribution, TG and IRI values were logarithmically transformed for statistical analysis. Pearson's correlation coefficients and partial correlation coefficients were calculated using the Stat View program for Macintosh (Abacus Concepts, Berkeley, CA). A P value less than .05 was considered significant for the two-tailed test.

RESULTS

General Characteristics

The subjects were characterized by normal body weight (BMI, 22.7 ± 2.5 kg/m^2), low to moderate body fat percentage (13.6% ± 4.0%), and normal WHR (0.80 ± 0.04). The mean $\dot{V}O_2$max was good (46.2 ± 6.3 mL/kg/min), but a wide range was observed (35.5 to 58.3). All had normal values for blood glucose, IRI, and C-peptide. In contrast, serum lipid levels varied, with some slightly above or below the normal range (Table 1).

Muscle Fiber Characteristics

The prevalence of type I, type IIa, and type IIx fiber was 41%, 39%, and 20%, respectively. A wide range was observed for both type IIa and IIx fibers (18% to 56% and 5% to 38%, respectively). The mean fiber areas were normal but the range was wide for all fiber types, with the largest fiber three times as big as the smallest. The mean value for the capillaries found around each fiber type was the same for all fiber types, as were the ranges, which were wide. This was also the case for the ranges regarding the cap/mm^2 and cap/fiber ratio. The diffusion index, ie, the mean area that each capillary supplied, showed similar values for the three fiber types, but a large range of values was observed, ie, about a fivefold difference was found between the lowest and the highest individual value (Table 2).

Relationships Between Metabolic Variables and Muscle Fiber Composition/Capillary Density

The serum level of LDL-C was associated inversely with the number of capillaries found around type IIx fiber ($r = -.50$, $P < .05$) and positively with the diffusion index of each fiber type ($r = .42$ to $.48$, $P < .05$). Serum LDL-C had an inverse but weak correlation with the number of capillaries around type I and type IIa fibers ($r = -.35$, $P = .08$ and $r = -.38$, $P = .06$, respectively), cap/mm^2 ($r = -.39$, $P = .05$), and cap/fiber ratio ($r = -.38$, $P = .06$). The apo B level correlated inversely with the number of capillaries found around each fiber type ($r = -.40$ to $-.54$, $P < .05$ to $.01$), cap/mm^2 ($r = -.54$, $P < .01$), and cap/fiber ratio ($r = -.40$, $P < .05$), and also correlated positively with the diffusion index of each fiber type ($r = .43$ to $.50$, $P < .05$ to $.01$) (Table 3). Figures 1 and 2 show the representative patterns for these correlations, and a good distribution of the data was observed. Furthermore, a positive correlation

Table 1. Characteristics of the Subjects

Characteristic	Mean ± SD	Range
Physical parameters		
Age (yr)	23.7 ± 3.5	18-36
BMI (kg/m^2)	22.7 ± 2.5	17.8-28.3
Body fat (%)	13.6 ± 4.0	9.6-24.8
WHR	0.80 ± 0.04	0.73-0.86
$\dot{V}O_2$max/weight (mL/kg/min)	46.2 ± 6.3	35.5-58.3
$\dot{V}O_2$max/lean weight (mL/kg/min)	53.2 ± 7.1	38.3-68.7
Blood parameters		
Cholesterol (mg/dL)		
Total	168.2 ± 59.4	144-237
LDL	94.7 ± 22.3	56-160
HDL	51.4 ± 13.7	34-90
HDL_2*	33.8 ± 9.3	21-50
HDL_3*	12.1 ± 1.8	10-15
Apolipoprotein (mg/dL)		
A-1	140.1 ± 32.4	48-222
B	75.4 ± 17.3	44-123
TG (mg/dL)	71.2 ± 32	35-146
Glucose (mg/dL)	79.4 ± 13.4	57-107
Insulin (μU/mL)	4.8 ± 2.5	2.3-13.8
C-peptide (μmol/L)	1.3 ± 0.5	0.7-2.7

*n = 14.

Table 2. Characteristics of the Skeletal Muscle Fiber

Characteristic	Mean ± SD	Range
Distribution in area (%)		
Type I	40.8 ± 10.3	16.3-62.0
Type IIa	39.0 ± 10.5	17.5-55.6
Type IIx	20.0 ± 9.2	5.1-38.4
Mean fiber area (μm^2)		
Type I	5,610 ± 1,650	2,903-10,239
Type IIa	5,987 ± 1,873	3,486-10,374
Type IIx	5,061 ± 1,918	2,998-11,041
No. of capillaries around the fiber		
Type I	4.37 ± 1.53	1.54-7.29
Type IIa	4.12 ± 1.26	1.72-6.16
Type IIx	3.67 ± 1.05	1.69-5.67
Mean	4.09 ± 1.27	1.80-6.24
Cap/mm^2	311 ± 127	115-556
Cap/fiber ratio	1.70 ± 0.52	0.76-2.81
Mean fiber area occupied by 1 capillary (μm^2)		
Type I	1,511 ± 868	697-3,923
Type IIa	1,563 ± 819	779-3,456
Type IIx	1,601 ± 955	696-4,223
Mean	1,539 ± 851	727-3,745

NOTE. The primarily denoted type IIb fibers in human skeletal muscle have been shown to resemble the type IIx fibers in rat muscle. Rat type IIb fibers have not been found in humans.

between the HDL2-C level and cap/mm^2 ($r = .64$, $P < .05$) and an inverse but weak correlation between the HDL2-C level and the diffusion index of each fiber type ($r = -.41$ to $-.48$, $P < .1$) were demonstrated (Table 3 and Fig 3). In contrast, there was no correlation between the fiber type and the lipid variables.

No differences in the variables for physical characteristics, blood chemistry, and muscle fiber morphology were found when comparing smokers and nonsmokers. The same was true for alcohol consumers and nonconsumers. The percent body fat was associated positively with the serum level of apo B ($r = .39$, $P = .05$), TG ($r = .54$, $P < .01$), and IRI ($r = .70$, $P < .001$) and inversely with $\dot{V}O_2max$ ($r = -.38$, $P = .06$). An

Table 3. Pearson's Correlation Coefficients and Partial Correlation Coefficients

	LDL-C		Apo B		HDL_2-C	
Parameter	Pearson r	Partial r	Pearson r	Partial r	Pearson r	Partial r
Capillaries around the fiber						
Type I	−.35	−.39	−.43*	−.42*	.20	
Type IIa	−.38	−.40*	−.40*	−.39	.32	
Type IIx	−.50*	−.50*	−.54†	−.53†	.21	
Cap/mm^2	−.39	−.43*	−.54†	−.55†	.64*	.70*
Cap/fiber ratio	−.38	−.38	−.40*	−.38	.17	
Diffusion index						
Type I	.42*	.49*	.44*	.51†	−.48	−.60*
Type IIa	.48*	.54†	.50*	.56†	−.41	−.55*
Type IIx	.42*	.49*	.43*	.51†	−.43	−.57*
Mean	.44*	.50*	.45*	.52†	−.43	−.56*

NOTE. Partial correlation coefficient was calculated after adjustment for age, $\dot{V}O_2max$, and percent body fat.

*$P < .05$.

†$P < .01$.

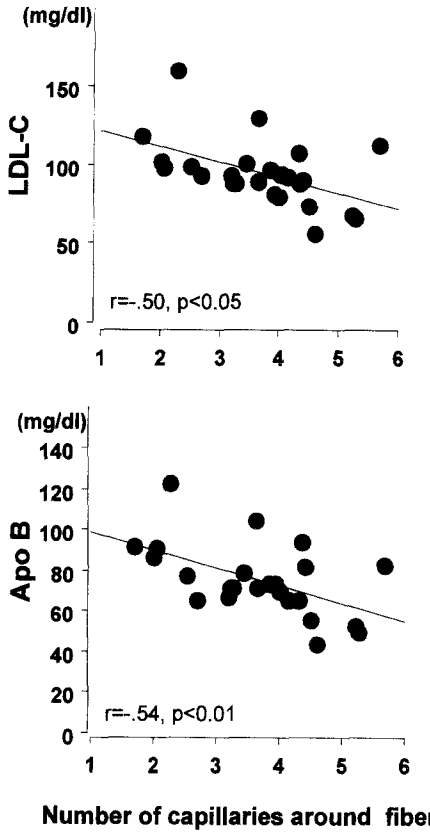

Fig 1. Relationship between the number of capillaries around the muscle fiber (type IIx) and serum LDL-C and apo B in 25 men.

inverse correlation was found between age and the number of capillaries around type I fiber ($r = -.46$, $P < .05$) and between age and cap/mm^2 ($r = -.44$, $P < .05$). Partial correlation analyses were performed to eliminate any possible confounding factors that may influence the relationships between muscle fiber morphology and the serum lipid level. Correlations between the capillary density/diffusion index and lipid variables remained or improved after adjusting for age, $\dot{V}O_2max$, and percent body fat (Table 3).

DISCUSSION

It is not clear whether muscle fiber capillary density influences serum lipoprotein and apolipoprotein levels. In the present study, we indeed demonstrate that skeletal muscle capillary supply had an inverse correlation and the diffusion index had a positive correlation with serum levels of LDL-C and apo B in 25 healthy men. Among 14 subjects, a positive correlation was also found between cap/mm^2 and HDL2-C. It is interesting that this relationship was demonstrated even after adjusting for possible confounding factors.

The atherogenic lipoprotein profile is defined as a constellation of elevated serum cholesterol, TG, and LDL and reduced HDL (in particular, large HDL2 subfraction).[20] We did not observe any correlation between serum TG and muscle capillary density.

The main issue to discuss in the present study is the reason that capillaries are more critical than fiber type. A large variation

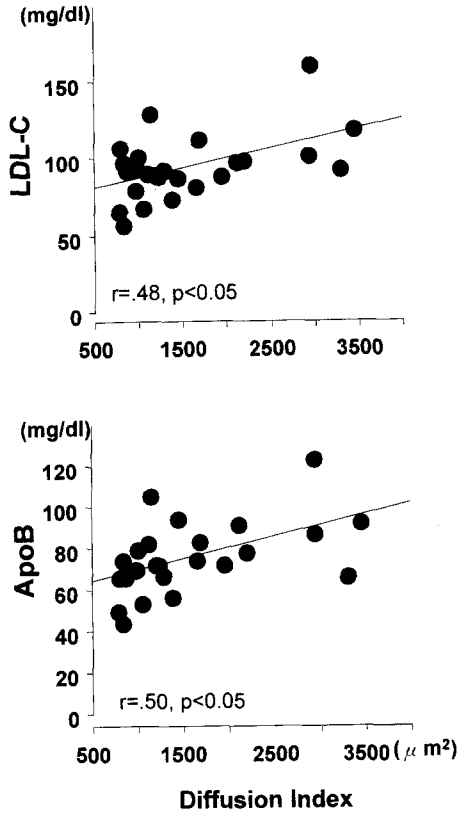

Fig 2. Relationship between the cross-sectional area occupied by 1 capillary (diffusion index) and serum LDL-C and apo B in 25 men (type IIa fiber).

exists not only in the fiber type proportion but also in the metabolic profile in humans.[21] A training study has demonstrated increased capillary density and a greater capillary supply in trained type IIa fiber versus untrained type I fiber.[22] In the present study, a wide range of values for the indices of capillary density were observed, and the differences among fiber types appeared small. It is possible that the influence of capillary density may overshadow the general property of the fiber type.

A closer correlation was found between lipid variables and diffusion indices than between lipid variables and other capillary density variables (Table 3). This finding may thus imply a difference in sensitivity among the indices, which might thus reflect metabolic conditions. It is estimated that the cap/mm^2 and cap/fiber ratio only describe the muscle as a whole. The number of capillaries around the fiber can be used to describe capillary supply to different fiber types. However, none of these variables can provide sufficient information with regard to the capacity for diffusion from the capillary to muscle fiber membrane.[22] The diffusion index, expressed as the mean fiber area occupied by one capillary, accounts for the difference in the diffusion capacity of each fiber type.[9]

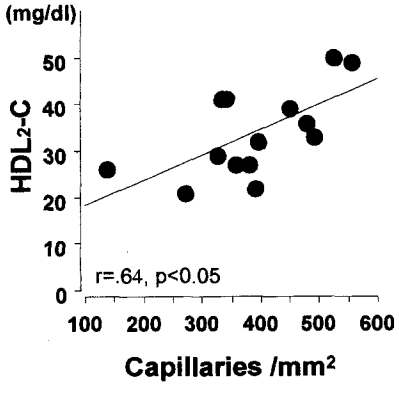

Fig 3. Relationship between the number of capillaries per mm^2 and serum HDL2-C in 14 men.

What is the mechanism of the relationships observed in this study? A possible explanation is that the decreased capillary density may contribute to the impairment of lipid metabolism via changes in the muscle blood flow, which could influence the supply of oxygen, substrates, and hormones and the enzyme activity. It has been suggested that muscle blood flow is an important determinant of peripheral HDL-C production to supply chylomicrons and other lipoprotein substrates for LPL.[23] Recently, skeletal muscle capillary density (cap/fiber ratio) has been demonstrated as a factor associated with both basal and insulin-stimulated blood flow in normal lean subjects.[24] Skeletal muscle LPL is known to exist on the endothelial surface of capillaries, and its activity is correlated with the percentage of type I fibers[10] and also with the capillary density.[11] The inverse associations between muscle LPL activity and serum LDL/VLDL-TG[25,26] and the positive association between muscle LPL activity and serum HDL2-C[27] have been demonstrated. In addition, exercise training increases muscle LPL activity, accompanied by a higher uptake of VLDL-TG and an increase of HDL-C production, in the trained leg.[28] Even short-term exercise training was recently demonstrated to induce an increase in muscle LPL gene expression.[29] Such evidence suggests the possibility that the combination of low capillary density with decreased capillary blood flow and decreased skeletal muscle LPL activity may impair the catabolism of LDL-C and the transport from HDL3-C to HDL2-C.

The muscle fiber distribution is considered a potentially important factor in determining serum lipoprotein levels.[5] The reason that we failed to confirm a relationship between the muscle fiber types and serum lipid levels as found in the previous study[5] may involve several factors: (1) the subjects of their study[5] were older than our subjects, including three groups with a wide variety of physical activity (joggers, sedentary subjects, and CHD patients); (2) the range for percent type I fiber was greater (12% to 88%) than in our study (16% to 62%); and (3) the correlation found in each group was weak or not significant, and only became significant when all subjects were grouped together.

Although genetic factors have been shown to influence the proportion of the fiber type,[30] it is of note that environmental factors can modify various muscle properties. The adaptive responses to exercise training seem to occur on different time scales.[31] The number of capillaries and the enzyme activity are affected more quickly than the fiber type composition. Although a switch from type IIx to type IIa can occur within weeks with an elevated enzyme activity, a further change from type IIa to

type I fiber occurs very slowly in man, if ever. These responses are also influenced by the type and intensity of training.

There is general agreement that physical activity/exercise training increases circulating HDL-C (particularly HDL2-C) and decreases LDL-C and TG, and skeletal muscles also play an important role in the control of lipid metabolism.[20] It is reasonable to presume that physical activity/exercise training can induce alterations in skeletal muscle characteristics such as changes in capillary density and oxidative capacity rather than a switch from type II to type I muscle fiber, and these may induce favorable metabolic conditions. However, we do not have any information about the causal relationships in this cross-sectional study.

In conclusion, the present findings indicate a close relationship between muscle fiber capillary density and serum levels of LDL-C, apo B, and HDL2-C in non-obese men. Muscle fiber capillary density is thus considered a possible influence on serum lipid levels. Finally, the causality and mechanism of this relationship need to be further investigated.

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