Body Weight, Skeletal Muscle Morphology, and Enzyme Activities in Relation to Fasting Serum Insulin Concentration and Glucose Tolerance in 48-year-old Men

H. LITHELL, F. LINDGÄRDE, K. HELLSING, G. LUNDQVIST, E. NYGAARD, B. VESSBY, AND B. SALTIN

SUMMARY

Tissue samples were taken from the gastrocnemius muscle of 26 randomly selected, glucose-tolerant, 48-yr-old men. Hexokinase, phosphorylase, lactate dehydrogenase (LDH), succinate dehydrogenase, and lipoprotein lipase activity (LPLA), as well as the area per fiber type and capillary density, were determined.

Mean fiber area correlated positively with relative body weight ($r = 0.53$, $P < 0.01$), but capillary density did not. The result is that, in cases of high body weight, each capillary supplies a larger muscle fiber area.

Serum insulin concentration in the fasting state correlated positively with body weight ($r = 0.77$, $P < 0.001$) and with mean fiber area per capillary ($r = 0.87$; $P < 0.001$). Only during the latter part of an oral glucose tolerance test (OGTT) did blood glucose concentrations correlate with relative body weight and mean fiber area per capillary ($r = 0.42$, $r = 0.51$, $P < 0.05$). A stepwise multiple regression analysis showed that the different muscle morphology measurements could account for 3/4 of the variation in the fasting serum insulin concentration, the fasting insulin/glucose ratio, and the blood glucose concentration at 120 min in the OGTT. Of the intracellular enzymes, only LDH ($r = -0.71$, $P < 0.001$) correlated with the mean fiber area per capillary.

LPLA correlated with capillary density ($r = 0.66$, $P < 0.001$), and, along with the muscle morphology measurements, could account for 3/4 of the variation in serum triglyceride concentrations.

The results show that a large mean muscle fiber area/capillary ratio indicates a morphologic imbalance, which is related to both glucose tolerance and various degrees of insulin sensitivity. **DIABETES *30*: 19–25, January 1981.**

From the Department of Geriatrics, University of Uppsala; the Department of Medicine, University of Lund, General Hospital, Malmö; and the Department of Clinical Chemistry, University Hospital, Uppsala, Sweden; and the A. Krogh Institute, University of Copenhagen, Denmark.
Address reprint requests to Hans Lithell, M.D., Department of Geriatrics, University of Uppsala, PO Box 12042, S-750 12 Uppsala, Sweden.
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Serum insulin concentration correlates with adipocyte size.[1] Furthermore, subjects with newly diagnosed, maturity-onset diabetes are more overweight than are nondiabetic individuals.[2] These relations point to a possible role of hypertrophic obesity in the precipitation of maturity-onset diabetes. It has been suggested that the development of overt, maturity-onset diabetes in obese subjects may be due to a relative insulin resistance in the peripheral tissues of these individuals, which results in a limited insulin production capacity becoming inadequate to meet the increased insulin demand.

There is also indirect evidence that the skeletal muscle contributes in a major way to both the glucose intolerance and the insulin resistance seen in obese individuals. In men who were physically active in their leisure time, the maximal oxygen uptake was higher and the serum insulin level lower during an oral glucose tolerance test (OGTT) than in physically inactive individuals.[3] Furthermore, when men with impaired glucose tolerance (IGT) were trained, both the serum insulin and the blood glucose values during an OGTT decreased.[4,5] We undertook the present study in a randomly selected group of middle-aged men to elucidate further the role of the skeletal muscle in regard to glucose tolerance and insulin resistance. Thus, the morphologic structure and enzyme levels of skeletal muscle, as well as some measurements of lipoprotein metabolism, were determined and related to glucose and insulin values in the fasting state and during an OGTT. In addition, reference values for various skeletal muscle variables are given for a population of middle-aged men.

SUBJECTS

The subjects were selected from men living in Malmö, Sweden, a city of 238,000 inhabitants. All men in this city born in 1929 or 1930 were invited to a health survey in 1977 and 1978. Seventy-five percent of the men accepted the invitation, and six to eight men per day (≅1200/yr) were examined for hypertension, alcoholism, and diabetes. For seven

consecutive days in the spring of 1978, the first four men to come each day were asked to participate in an enlarged study. This included a muscle biopsy and additional blood samples, which were also performed after an overnight fast. All but one of the 28 men invited agreed to participate. However, the number of participants is 26 instead of 27, as it was found that one subject was not in the fasting state during the second test. Since large tissue samples were needed for the extended morphologic studies of muscle, the tissue specimens were of adequate size in only 17 subjects.

PROCEDURE

First visit. After an overnight fast, the men were subjected to an OGTT (30 g/m^2 body surface). Capillary blood samples were taken at 0, 20, 40, 60, 90, and 120 min for blood glucose determination and venous blood samples at 0, 40, and 120 min for plasma insulin determination. After the OGTT, a submaximal work test was performed. A questionnaire was also completed. Body weight and height were measured. Serum triglyceride concentrations were determined on fasting blood samples.

Second visit. On this occasion, venous blood was drawn in the fasting state for determination of serum insulin, plasma glucagon, serum triglycerides and cholesterol, serum apolipoproteins B and A-I, and plasma C-peptide. The muscle biopsy was taken with a needle[6] from the lateral head of the gastrocnemius muscle. A bundle of muscle fibers was dissected out, mounted for histochemical studies in a plastic material (tissue-Tec), and frozen in isopentane cooled with liquid nitrogen. The remaining portion of the muscle piece was carefully freed from visible fat, connective tissue, and blood and was frozen in liquid nitrogen. The following muscle enzymes were determined: hexokinase, phosphorylase, lactate dehydrogenase, and succinate dehydrogenase. An additional piece of muscle was washed in saline, dried on filter paper, and frozen in liquid nitrogen. This piece was used for the determination of lipoprotein lipase activity. All muscle samples were stored at −80°C until analyzed.

METHODS

The submaximal work test was performed on a mechanically braked cycle ergometer (Monark). From the submaximal heart rate response, the subjects' maximal oxygen uptake ($\dot{V}_{O_2}$max) was estimated.[7] Serum triglyceride and cholesterol concentrations were determined on a Technicon AutoAnalyzer II.[8] Apolipoproteins B and A-I were determined by electro-immunoassay, as described earlier.[9] The apolipoprotein concentrations in serum are expressed in arbitrary units (AU) relative to the concentration in a reference serum obtained from a large pool of healthy blood donors (100 AU). The apolipoprotein concentrations in this reference serum, when standardized against a lipoprotein B preparation (density = 1.030-1.050) and a highly purified apolipoprotein A-I preparation, were estimated to be 1.0 and 1.5 mg/ml, respectively. Blood glucose was measured according to Carrol et al.[10] Relative body weight was estimated according to the formula of actual (measured) weight to ideal body weight for body height. The tables of Lindeberg et al.[11] were used as the ideal weight reference.

Serum insulin was analyzed according to Heding[12] in samples from the OGTT. To increase the sensitivity in the low physiologic range, a modified, radioimmunosorbent technique (Phadebas, Pharmacia Diagnostics AB, Uppsala, Sweden) was used when analyzing the fasting insulin concentration on samples from the second visit. The latter samples were preincubated with the matrix-bound antibodies for 24 h before the isotope-labeled insulin was added. The coefficient of variation was 5% in the range of from 5 to 10 mU/L. Plasma C-peptide was determined using a radioimmunoassay, according to Heding.[13] Plasma glucagon was analyzed according to Unger et al.[14] using glucagon antiserum 30 K, which is specific for pancreatic glucagon.[15] Plasma samples were collected, stored, and analyzed as earlier described.[16] The coefficient of variation over the working range (10-1000 ng/L) was 12.5%.

The heparin-elutable portion of the lipoprotein lipase was determined using a method described earlier[17] with some modifications. The stock emulsion, thus, contained triglycerides (40 g/L) and egg phospholipids (2.4 g/L); the final triglyceride concentration in the reaction medium was 3 mmol/L. The heparin concentration was 200 IU/ml. Enzyme activity is expressed as milliunits per gram (1 mU = 1 nmol of fatty acid released per minute).

Measurement of activities for hexokinase, phosphorylase, lactate dehydrogenase, and succinate dehydrogenase in the muscle was based on the principle described by Lowry and Passonneau,[18] with fluorometric determination of the NAD-NADP–coupled reaction, as described by Essén.[19] The reason for choosing these four enzymes is that the cytoplasmic enzymes determined represent different parts of the glycolytic pathways, while SDH activity is used as a marker of mitochondrial potential, as its activity is closely related to other mitochondrial enzymes.[20]

Water content of the muscle samples was obtained by a weighing-drying procedure and the protein content was determined according to Lowry et al.[21] Both the water and the protein content of the muscle samples were in the normal range, mean values being 75.8 ± 0.8% and 183 ± 5 mg/g muscle tissue, respectively. Thus the enzyme activities are expressed per unit wet weight of the muscle tissue.

The samples for histochemical analysis were cut at −20°C. Serial sections were stained for capillaries[24] and for myofibrillar ATPase after preincubations at pH 10.3,[22] 4.6, and 4.3.[23] The relative occurrences of slow twitch (ST) and fast twitch (FT*a* and *b*[25]) fibers and their sizes were calculated, as were the relative areas they occupied in the muscle. The number of capillaries and fibers per square millimeter and the number of capillaries around each fiber (type) were determined. The number of capillaries could then be expressed per fiber-type area or per mean fiber area.

STATISTICS

Statistical calculations were made according to Snedecor and Cochran.[26] Because of skewed distributions, mean values were calculated both before and after the logarithmic transformation of data. Several relationships were not linear, so the coefficients of correlation were calculated on logarithmically transformed data and after pairwise elimination of missing data. Thus the number of subjects is 26, except when muscle morphologic variables (fiber composition, area, and capillary content) or muscle enzymes are included. In these latter cases, the number of subjects varied between 17 and 23. A stepwise, multiple regression anal-

ysis was performed, entering variables according to their degrees of partial correlation.[27] The effect of smoking was tested using a one way analysis of variance.

RESULTS

The following results refer to a group of 26 men of whom none was overtly diabetic or had impaired glucose tolerance.[28] The mean value for fasting blood glucose was 5.0 mmol/L (range, 3.8-5.8), and at 120 min in the OGTT it was 4.7 mmol/L (range, 2.4-6.4).

Physical characteristics. The mean body height was 180 cm and mean body weight, 80.4 kg; the mean relative body weight was 1.09, with a range of from 0.85 to 1.48 (Table 1).

The estimated, maximal oxygen uptake ($\dot{V}_{O_2}$max) averaged 3.2 L/min or 39 (23-52) ml/kg/min. The influence of different degrees of daily physical activity on various laboratory variables could not be evaluated. Only four subjects reported that they were physically active in their leisure time and only five performed heavy manual work. This fact limited the possibilities of obtaining statistically significant correlations with other variables. The physical activity pattern and mean values for body stature and work capacity are similar to those found in a large sample of the same population.[3]

Muscle morphology and enzyme activities. The typing of the muscle fibers of the gastrocnemius muscle showed that, on average, 53% was of the ST type and the FT fibers were equally divided into FT*a* and FT*b* types. The sizes of these fiber types averaged 4900, 5600, and 5600 μm^2 (ST, FT*a*, FT*b*), with noticeable variations around these means (Table 2A).

The mean values for the number of capillaries and muscle fibers per square millimeter were 312 and 212, respectively, which yielded 1.5 capillaries per fiber (Table 2B). Each fiber type was surrounded by 4.1 (ST), 3.9 (FT*a*), and 3.5 (FT*b*) capillaries. Taking into account the average fiber area of each fiber type (Table 2A), each capillary supplied, on the average, 1100, 1200, and 1500 μm^2 of ST, FT*a*, and FT*b* fibers, respectively (Table 2B).

No significant relationships existed between body size, $\dot{V}_{O_2}$max, and muscle fiber composition. Muscle fiber size, however, related to body weight. This relationship existed for each fiber type as well as for the mean fiber area ($r = 0.51$, $P < 0.05$). Relative body weight also related to muscle fiber size ($r = 0.53$, $P < 0.01$) (Figure 1).

Capillary content of the muscle, expressed as capillaries per square millimeter or per fiber, was only weakly related to $\dot{V}_{O_2}$max, and these relationships were not improved when the area of the fibers was taken into account. The closest relationships between any variable expressing capillary content and the other variables studied were between the mean fiber each capillary had to supply and the relative body weight ($r = 0.81$, $P < 0.001$), and the measured body weight ($r = 0.74$, $P < 0.001$).

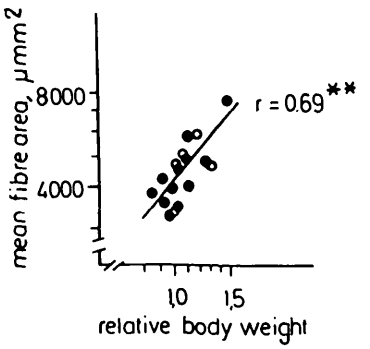


FIGURE 1. Relationship between the relative body weight and the mean muscle fiber area. Open symbols indicate non smokers, and solid symbols, smokers. Results are given for the 17 men, also depicted in Figures 2 and 3, on whom muscle capillary data were available. On six more men (N = 23), muscle fiber areas were determined. There is a significant correlation when N = 17 as well as when N = 23, but the *r* value is slightly higher with the lower number of subjects (compare text). The explanation for this difference is most likely the high technical quality of the sections (good stain, perfect cross section) we have in 17 subjects and needed to accurately count the capillaries may also have brought about a more accurate area determination.

The mean values for the activity of the glycolytic enzymes hexokinase, phosphorylase, and lactate dehydrogenase were 1.0, 8.6, and 210 mmol/kg/min, respectively (Table 2C). The only mitochondrial enzyme measured was succinate dehydrogenase, and its activity averaged 7.5 mmol/kg/min. The relationship between the succinate dehydrogenase activity and the maximal oxygen uptake (expressed in ml/kg/min) was quite close ($r = 0.88$, $P < 0.001$).

Lipoprotein lipase activity (LPLA) in skeletal muscle averaged 45 mU/g, with a range of from 16 to 107 mU/g. The mean value is higher than that described earlier for tissue taken from the lateral vastus muscle,[16] but the results are not directly comparable because of the modified methods used (see under METHODS). The LPLA in skeletal muscle correlated inversely with both the relative body weight ($r = -0.56$, $P < 0.01$) and the mean cross-sectional area of the muscle fibers ($r = -0.58$, $P < 0.01$). Furthermore, a correlation was found between the LPLA and the capillary density ($r = 0.66$, $P < 0.001$) and mean fiber area per capillary ($r = -0.66$, $P < 0.001$) (Figure 2). There was no relationship between LPLA and fiber composition.

TABLE 1
Variables describing body stature and maximal oxygen uptake capacity ($\dot{V}_{O_2}$ max)

	Body height (cm)	Body weight (kg)	Relative body weight	$\dot{V}_{O_2}$ max	
				l/min	ml/kg/min
Mean	179.9	80.4	1.09	3.2	39.2
SD	7.1	13.3	0.15	0.8	7.1
Range	168.0–198.0	57.4–115.5	0.85–1.48	2.0–4.5	23.0–52.0
N	26	26	26	25	25
$Mean_{log}$*	179.9	79.4	1.07	3.1	38.5

* $Mean_{log}$ indicates the antilog value of the mean value calculated after log transformation of the individual values.

TABLE 2A
Relative occurrence of slow twitch (ST = type 1) fibers, fast twitch (FT) fibers of the *a* (type IA) and *b* (type IIB) type, mean fiber area for each fiber type, and the mean value of fiber area, taking the occurrence of the three fiber types into consideration (N = 23)

	Relative (%) Occurrence			Mean Fiber Area (μm^2)			
	ST	FT*a*	FT*b*	ST	FT*a*	FT*b*	Mean
Mean	53.1	22.5	23.7	4942	5567	5555	5154
SD	16.7	9.3	11.6	1414	2244	2171	1608
Range	28.0–86.0	7.0–41.0	2.0–40.0	2938–7596	3059–11,442	2516–10,573	3278–8707
N	23	23	23	23	23	23	23
$Mean_{log}$*	50.6	20.5	19.6	4753	5212	5188	4932

* $Mean_{log}$ indicates the antilog value of the mean value calculated after log transformation of the individual values.

TABLE 2B
The density of capillaries and muscle fibers per square millimeter, the mean number of capillaries around each slow twitch (ST) and fast twitch (FT) fiber of the *a* and *b* type (several fibers can share one capillary). The mean fiber area of ST, FT*a*, and FT*b* fibers per capillary and the mean value for all fiber types, taking the relative occurrences of the three fiber types into consideration (N = 17)

	Capillaries per mm^2	Muscle fibers per mm^2	Cap./fiber	Capillaries around each fiber type			Mean fiber area (μm^2) per capillary			
				ST	FT*a*	FT*b*	ST	FT*a*	FT*b*	Mean
Mean	312	212	1.5	4.1	3.9	3.5	1084	1198	1478	1197
SD	53	36	0.3	0.7	0.6	0.7	171	226	333	211
Range	233–421	168–312	0.9–2.0	3.2–5.6	3.0–5.0	2.4–4.6	887–1532	878–1522	984–2135	955–1737
$Mean_{log}$*	308	206	1.4	4.1	3.9	3.4	1071	1178	1445	1180

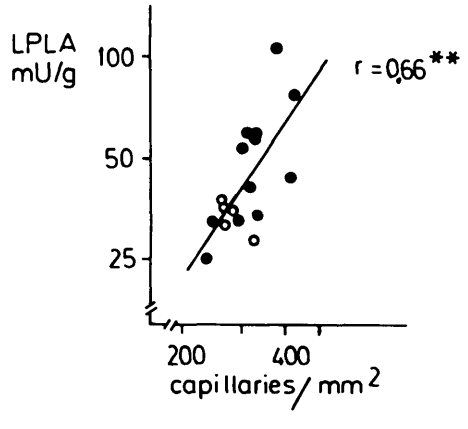
* Mean log indicates the antilog value of the mean value calculated after log transformation of the individual values.

TABLE 2C
The lipoprotein lipase activity (LPLA) [mU/g, one milliunit (mU) signifying the release of 1 nmol of fatty acid per minute] and the activities of succinyl dehydrogenase (SDH), hexokinase (HK), phosphorylase (phosph.), and lactate dehydrogenase (LDH), all expressed in millimoles (of converted substrate) per kilogram of tissue and per minute

	LPLA mU/g	SDH mmol/kg/min	HK mmol/kg/min	Phosph. mmol/kg/min	LDH mmol/kg/min
Mean	45	7.54	1.04	8.55	210
SD	19	1.61	0.17	1.31	30
Range	16–107	4.7–10.2	0.69–1.35	6.0–11.6	160–260
N	26	24	20	20	19
$Mean_{log}$*	42	7.36	1.02	8.45	210

* $Mean_{log}$ indicates the antilog value of the mean value calculated after log transformation of the individual values.

FIGURE 2. Relationship between the number of capillaries per square millimeter of muscle, cross sectional area, and the lipoprotein lipase activity (LPLA) per gram of muscle in 17 middle-aged men. Symbols are as in Figure 1.



LPLA correlated inversely with serum insulin in the fasting state ($r = -0.50$, $P < 0.01$) and at 120 min during the OGTT ($r = -0.54$, $P < 0.01$). There was no relationship with blood glucose in the fasting state or during the first 90 min of the OGTT, but with the value at 120 min there was a significant, inverse correlation ($r = -0.64$, $P < 0.001$). LPLA did not correlate with plasma glucagon values.

BLOOD ANALYSES

Glucose tolerance. In this random sample of normoglycemic and glucose-tolerant men, blood glucose in the fasting state and at 120 min in the OGTT related similarly to relative body weight and muscle morphology measurements. The best correlation was found between blood glucose at 120 min and the mean fiber area per capillary ($r = 0.51$, $P < 0.05$). Although the blood glucose values during the OGTT were not or only weakly correlated to the mean fiber area per capillary, there was a definite pattern. The closest correlations were found before any glucose was given (fast-

TABLE 3
The concentration in blood plasma of insulin in the fasting state and at 40 to 120 min in the oral glucose tolerance test (OGTT), as well as fasting levels of glucagon, C-peptide, triglycerides (TG), cholesterol, and apolipoproteins (apo) A-I and B

	Serum Insulin (mU/L)								
		During OGTT							
	Fasting	40 min	120 min	Glucagon (pg/L)	C-peptide (nmol/L)	TG (mmol/L)	Chol (mmol/L)	Apo A-I (AU)†	Apo B (AU)
Mean	11.3	83.2	23.6	148	0.84	2.4	5.3	88	114
SD	7.5	38.2	19.9	78	0.33	0.6	0.8	14	23
Range	4.3–36.4	21–200	3–91	34–355	0.52–1.70	1.3–3.8	3.6–6.9	66–125	74–158
N	26	26	26	26	26	26	26	26	26
$Mean_{log}$*	9.7	75.2	17.4	129	0.79	2.3	5.3	86	111

* $Mean_{log}$ indicates the antilog value of the mean value calculated after log transformation of the individual values.
† Arbitrary units.

ing blood glucose) and during the last 30 min of the OGTT.

Serum insulin and plasma glucagon. The mean value of fasting serum insulin was 11.3 mU/L, with a noticeably large range (Table 3). The fasting, serum insulin concentration correlated with the relative body weight ($r = 0.77$, $P < 0.001$). When the relationships to different muscle morphology measurements were tested, a correlation was found with the mean fiber area ($r = 0.54$, $P < 0.01$). The relationship improved when the capillary density ($r = -0.60$, $P < 0.01$) was taken into account, but the best correlation was found with the mean fiber area per capillary ($r = 0.87$, $P < 0.001$) (Figure 3). The serum insulin at 40 and 120 min during the OGTT showed only weak relationships with body weight, relative body weight, or with muscle morphology measurements. Plasma glucagon did not relate to relative body weight or muscle morphology measurements.

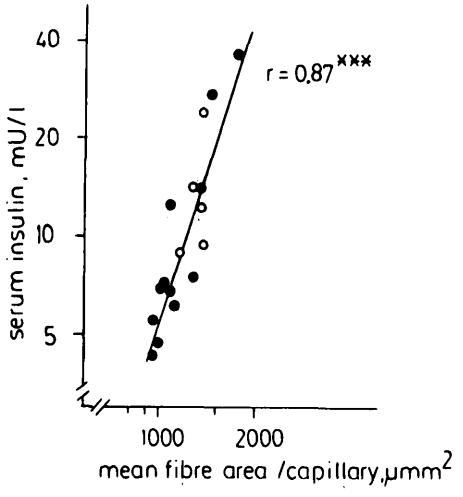
Insulin/glucose ratio. The ratio between the serum insulin and the blood glucose concentrations had the best positive correlation with the mean fiber area per capillary in the fasting state ($r = 0.88$, $P < 0.001$).

The concentration of C-peptide in plasma correlated closely with the fasting serum insulin concentration ($r = 0.89$, $P < 0.001$).

Serum lipids and apolipoproteins. The mean value of the serum triglyceride concentrations was 2.4 mmol/L. From 1970 to 1973, when 49 and 50-yr-old men in Uppsala, Sweden, were examined for cardiovascular risk factors,[24] the mean value of serum triglycerides was 2.0 mmol/L. Although the mean value is fairly high, there were no subjects with extreme hypertriglyceridemia in this population (Table 3). The serum cholesterol concentration averaged 5.3 mmol/L, and the concentrations of apolipoproteins A-I and B were, on the average, 88 and 114 AU, respectively (Table 3).

Effect of smoking. Nonsmokers ($N = 7$) differed significantly from smokers with regard to the serum insulin concentration and the insulin/glucose ratio at 120 min in the OGTT (higher in nonsmokers) and with regard to the LPLA (lower in nonsmokers). The average number of capillaries per square millimeter was 269 in nonsmokers and 325 in smokers, the difference being not significant ($0.05 < P < 0.10$).

FIGURE 3. Relationship between the mean fiber area per capillary and the serum insulin concentration in 17 middle-aged men. Symbols are as in Figure 1.



STEPWISE, MULTIPLE REGRESSION ANALYSIS

The variation in relative body weight could explain 66% of the variation in mean fiber area per capillary. For ST fibers alone (area per capillary), 72% of the variation was accounted for by the variation in relative body weight.

Serum insulin. Muscle morphology measurements alone could explain 81% of the total variation of the fasting, serum insulin concentration. Relative body weight contributed independently of muscle morphology measurements, so that together they accounted for a total of 95% of the variation of fasting serum insulin.

Blood glucose at 120 min in the OGTT. Muscle morphology measurements alone explained 74% of the variation in the concentration of blood glucose at 120 min in the OGTT. Relative body weight did not contribute to the variation independently of muscle morphology measurements.

The ratio between insulin and glucose concentrations before any glucose was given was explained primarily by muscle morphology variables (81%) and relative body weight (92% total). The ratios at 40 and 120 min after glucose was given were accounted for in a similar manner with muscle morphology measurements, yielding 22% and 44% of the variation and increasing to 45% and 53% when relative body weight was added as an independent variable.

LPLA. The number of capillaries per square millimeter accounted for 44% of the variation of the LPLA in the population. Other variables describing muscle morphology increased that percentage, so that a total of 61% of the

variation was then explained. Body weight or relative body weight contributed independently of the muscle morphology measurements to account for a further 7% of the variation of LPLA.

Serum triglyceride concentration. The stepwise, multiple regression analysis showed that LPLA and muscle morphology measurements together explained about 75% of the serum triglyceride variation, both from the first and the second visit. Relative body weight contributed a further 10%, so that a total of 85% of the variation of serum triglycerides was explained by these variables.

DISCUSSION

The pathogenesis of adult-onset diabetes mellitus is complex and, in part, unknown. A hereditary factor exists. A striking feature in many patients is a peripheral insensitivity to insulin (for other references, see ref. 30). In such cases the number of insulin receptors is decreased, but this may well be a state of decompensation rather than a primary feature.[31] There are several indications that the site for the insulin insensitivity is found not only in adipose and liver tissue but also in skeletal muscle. Observations in obese mice indicate a decreased intrinsic glucose conversion to glycogen in skeletal muscle, which could, in part, explain the insulin resistance.[32] However, at present it is not possible to decide which, if any, of these factors is primary.

In the present study, glucose tolerances, as measured by the blood glucose values at the end of the OGTT, correlated with muscle morphology measurements. The best of those correlations pertained to the cross section area of the fibers and to the density of the capillaries (e.g., the mean fiber area per capillary). The serum insulin concentration and the insulin/glucose ratio in the fasting state also correlated with the mean fiber area. Indeed, the multiple regression analysis showed that the muscle morphology measurements alone could explain about 75% of these expressions of glucose tolerance and insulin sensitivity. The relative body weight accounted for part of the variation of the serum insulin concentration and the insulin/glucose ratio in the fasting state, indicating that the adipose tissue (independent of skeletal muscle) contributes to the variations.

The present data suggest that subjects with relatively large body weights have enlarged leg muscle fibers, as determined from cross sectional measurements. Muscle hypertrophy results from high tension development,[33] which may mean that only rather infrequent, but fast or strong, contractions are needed to enlarge the size of the muscle fibers. In this type of contraction, FT fibers are recruited.[34] In contrast, the capillary density increases only after endurance-type training, i.e., repetitive, light, dynamic contractions.[35] This implies that, in subjects with large (or increasing) body weight, some brief and strong contractions are performed during the day, which may be sufficient to maintain or enlarge the fiber area (especially the FT fibers) without a concomitant increase of capillary density. This enlargement of the muscle cells causes a relative decrease in the density of the capillaries, so that each capillary has a larger muscle area to supply.

Of the intracellular muscle enzymes studied, the succinate dehydrogenase activity, as anticipated, related to the physical work capacity of the subjects,[20] but the glycolytic enzymes did not. The succinate dehydrogenase, hexokinase, and phosphorylase activities did not relate to any measurements of muscle fiber size. This could speak in favor of an enhancement of some energy-liberating metabolic pathways which, at least in part, are linked to the growth of the muscle fiber. A similar situation was found for adipocytes, where the metabolic activity is related to the cell size.[36]

In men with established, impaired glucose tolerance (IGT), hexokinase and succinate dehydrogenase were decreased.[4] Both these enzyme activities increased with endurance-type training, during which glucose tolerance improved and serum insulin concentrations decreased.[4] These latter data support the view that postreceptor mechanisms in the muscle tissue are of importance in regulating glucose tolerance and insulin resistance. However, a change in the morphology of the muscle tissue (which is influenced by physical training[24] and also by body weight, as shown in the present study) may precede the decline of the metabolic potential in the muscle fibers associated with IGT.

Our data strongly suggest that the diffusion distances within the skeletal muscle (in this study, being measured as the mean muscle fiber area per capillary) are linked to the different degrees of glucose tolerance and insulin sensitivity found in these individuals. One would then anticipate a quite large diffusion distance in the muscle of men with IGT. However, this is not what was found.[4] On the other hand, some skeletal muscle capillaries from the men with IGT had an abnormal stain. This may indicate some dysfunction which so far has not been evaluated. The possibility exists that men with IGT have a low number of normally functioning capillaries.

LPLA in muscle tissue has earlier been described to correlate inversely both with relative body weight and with fasting serum insulin concentration.[37] In obesity there is a changed glucagon and insulin concentration ratio. This, in turn, could have had a regulatory effect on the synthesis of lipoprotein lipase, as glucagon (but not insulin) stimulates lipoprotein lipase synthesis in rat muscle tissue.[38] However, the present results indicate that the relationship between LPLA and insulin is derived from the fact that both depend on the muscle fiber size and the degree of capillarization. Lipoprotein lipase is thought to be synthesized within the muscle cell, to be transported from the cell, and then to adhere to glucose-aminoglycans at the surface of endothelial cells of surrounding capillaries.[39] This endothelial-bound, lipoprotein lipase is the part which is physiologically active in hydrolyzing serum triglycerides. It can also be released by heparin, a fact which was taken advantage of in the method for determining LPLA applied in this study. The present results imply that the capillary density determines to a large extent how much heparin-releasable LPLA can be measured in the tissue. Both factors may be quantitatively important in the regulation of the serum triglyceride concentration.

In the present study, we show a close relation between the area in the skeletal muscle that each capillary has to supply and measurements of glucose tolerance, insulin sensitivity, and triglyceride metabolism. The mean fiber area per capillary, in turn, related closely to the relative body weight. The data point to the possibility that a low capillary density in skeletal muscle might be an early characteristic of relative obesity, contributing to the reduced glucose tolerance, in-

sulin sensitivity, and hypertriglyceridemia often found in this state.

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