Effects of Body Composition on Insulin Sensitivity

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SUMMARY

We studied the effects of body composition and maximal aerobic power on insulin sensitivity in 23 normal-weight, healthy male subjects. Eight were weight lifters, eight were long-distance runners, and seven were untrained controls. In each subject, the percentage of body weight (BW) made up of muscle and fat tissue (% muscle and % fat, respectively), the maximal aerobic power ($\dot{V}O_2$max), and the tissue sensitivity to insulin were measured. The weight lifters were characterized by 35% higher % muscle as compared with the runners or controls ($P < 0.01$). $\dot{V}O_2$max in the runners was 30–40% higher than in the weight lifters or controls ($P < 0.001$). During the euglycemic clamp studies, similar steady-state plasma glucose and insulin levels were achieved in each group. When calculated per total BW, the rate of glucose metabolism (M) was virtually identical in the weight lifters (10.26 ± 1.02 mg/kg BW/min) and the runners (10.03 ± 0.86 mg/kg BW/min), and 40–45% higher than in the controls (7.10 ± 0.75 mg/kg BW/min, $P < 0.05$). When calculated per muscle mass (M_m), only the runners had a higher than normal rate of glucose metabolism ($P < 0.02$). M was directly proportional to % muscle ($r = 0.54$, $P < 0.01$) and inversely related to % fat ($r = -0.72$, $P < 0.001$). The multiple linear regression analysis revealed a highly significant multivariate correlation between M and the combined effect of % muscle, % fat, and $\dot{V}O_2$max ($r = 0.78$, $P < 0.0005$). In addition, a regression equation for the predicted M was obtained as follows: M (mg/kg BW/min) = 0.697 + 0.155 · % muscle − 0.312 · % fat + 0.065 · $\dot{V}O_2$max (ml/kg/min).

In conclusion, first, body sensitivity to insulin is directly related to muscle mass and inversely proportional to adiposity. Second, it may be possible in healthy man to predict the rate of glucose metabolism when body composition and $\dot{V}O_2$max are known. DIABETES *32*:965–969, October 1983.

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Received for publication 31 December 1982 and in revised form 31 March 1983.

Insulin resistance is associated with conditions such as obesity,[1–3] aging,[4–6] or physical inactivity.[7] The mechanisms of decreased insulin action in these patients are not known. Although insulin binding to receptors may be reduced in obesity,[1,2] this is not a uniform phenomenon,[8] and in the aged[5] or during physical inactivity[9] insulin binding is unaltered. In each of these conditions the relative contribution of muscle tissue to total body weight (BW) is diminished and adipose tissue is enhanced. Since insulin resistance is a consequence of a reduced glucose uptake by peripheral tissues, mainly muscle,[2] one would anticipate that a decrease in muscle mass leads to a reduced body sensitivity to insulin. On the other hand, physical training, which is associated with an increase in muscle mass, also results in augmented body sensitivity to insulin.[10–12] In overweight patients, insulin response to oral glucose load is smaller in muscular than obese subjects in the face of similar glucose tolerance,[13] thus suggesting enhanced insulin sensitivity in the presence of large muscle mass. The effect of body composition on insulin sensitivity has not been examined in non-obese subjects with the use of the direct measurements of glucose uptake during physiologic hyperinsulinemia. Consequently, we determined insulin sensitivity in healthy subjects with normal total body weight but a wide range of different body compositions.

METHODS

SUBJECTS

Twenty-three men were studied. Eight were weight lifters, eight were long-distance runners, and seven were untrained control subjects. Their age and body dimensions are shown in Table 1. The weight lifters engaged in weight lifting 3–5 times per week. The runners' exercise program consisted of running 7 miles or more per day six to seven times per week. Both groups had been training at least 5 yr before the study. The controls did not engage in athletics on a regular

TABLE 1
Body composition and $\dot{V}O_2$ max of the subjects (mean ± SEM)

	Weight lifters	Runners	Controls
Age (yr)	24 ± 1	24 ± 1	24 ± 1
Height (cm)	181 ± 1	181 ± 2	179 ± 1
Weight (kg)	80 ± 3	69 ± 1*	79 ± 2
% IBW†	110.6 ± 2.4	97.1 ± 2.7‡	112.7 ± 1.7
Absolute muscle mass (kg)	43.1 ± 2.8‖	27.7 ± 1.6	30.1 ± 1.2
% Muscle	53.6 ± 2.1§	40.2 ± 1.7	39.3 ± 1.5
Absolute fat mass (kg)	4.3 ± 1.7	3.9 ± 1.7	8.3 ± 2.5¶
% Fat	5.4 ± 0.8	5.7 ± 0.8	10.1 ± 1.2¶
$\dot{V}O_2$ max (ml/kg/min)	54.9 ± 2.9	71.5 ± 1.9#	50.2 ± 1.9

*$P < 0.01$ versus weight lifters and versus controls.
†Metropolitan Life Insurance Tables, 1958.
‡$P < 0.01$ versus weight lifters; $P < 0.001$ versus controls.
§$P < 0.001$ versus runners and versus controls.
‖ $P < 0.001$ versus runners; $P < 0.002$ versus controls.
¶$P < 0.01$ versus weight lifters and versus runners.
#$P < 0.001$ versus weight lifters and versus controls.

basis. None of the subjects was taking any medications at least 3 wk before the study. For 2 days before the study, the subjects ingested a weight-maintaining diet containing 200–250 g carbohydrate/day. The nature, purpose, and possible risks of the study were explained to all subjects before they gave their voluntary consent to participate.

MEASUREMENTS

In vivo sensitivity to insulin. In each subject, the sensitivity to insulin action in vivo was determined using the euglycemic clamp technique.[14] The subjects were studied in the postabsorptive state at 8 a.m. after a 10–12-h overnight fast. An indwelling catheter was inserted in an antecubital vein for glucose and insulin infusions. A second catheter was inserted retrograde into a hand vein for blood sampling. The hand was then inserted into a heated chamber in which the air temperature was maintained at 70°C to ensure arterialization of venous blood.[15] A priming plus continuous infusion of crystalline porcine insulin (Actrapid, Novo, Copenhagen, Denmark) was given. The priming dose was infused in a logarithmically falling manner for 10 min to reach the hyperinsulinemic level. The continuous steady-state infusion was begun at 10 min and continued for 110 min to maintain the hyperinsulinemia. The rate of the continuous infusion was 40 mU/m^2 · min in all subjects, resulting in a plasma insulin concentration of approximately 85 mU/L. The plasma glucose concentration was maintained at the fasting level by determination of plasma glucose concentration every 5 min from the arterialized venous blood ($paO_2 > 85$ mm Hg) and the periodic adjustment of a variable infusion of 20% glucose solution. During euglycemic hyperinsulinemia, the amount of glucose infused serves as a measure of glucose taken up by the cells and can thus be used as a measure of whole body sensitivity to insulin. The rate of glucose uptake during hyperinsulinemia was determined during the 20–120-min period.

Estimation of body muscle mass. The muscle area of the upper extremity (AMA) was estimated from measures of upper arm circumference (AC, mm) and triceps skinfold (TSF, mm). Skinfold thicknesses were determined using Harpenden callipers (M-13, John Bull, British Indicators Ltd., United Kingdom). All measurements were done in triplicate by the same person on the dominant side of the body. AMA was calculated according to the formula of Jelliffe et al.[16] as follows:

$$\text{AMA (cm), for men} = \frac{(AC - \pi TSF)^2}{4\pi} - 10$$

Total body muscle mass was estimated according to the formula of Heymsfield et al.:[17] total body muscle mass (TBM, kg) = height (0.0264 + 0.0029 × AMA). The formula is based on correlation between AMA and 24-h urinary creatinine excretion.[16] Percentage of BW made up of muscle tissue (% muscle) was calculated by dividing TBM by BW (× 100).

Estimation of body fat. Percentage of BW made up of fat tissue (% fat) was estimated from the sum of six skinfolds measured from triceps, subscapular, pectoral, umbilical, suprailiac, and thigh regions. The values of the six skinfolds were summed up and 8 mm was subtracted to correct for the nonadipose content of the skinfolds. The corrected skinfold total was divided by BW to obtain skinfold/BW ratio (R). Percentage of fat was calculated as follows: % fat = 11.5453 × R − 0.2838.[18]

Maximal aerobic power. In each subject the maximal aerobic power ($\dot{V}O_2$max) was determined by a standard incremental exercise test on a cycle ergometer.[19]

Analytic procedures. Plasma glucose was measured with the glucose-oxidase method (Beckman Glucose Analyzer II, Beckman Instruments Corp., Fullerton, California). Plasma insulin concentration was measured by radioimmunoassay.[20] Statistical comparisons between groups were made using the analysis of variance. Multiple linear regression analysis, simple and partial correlation coefficients, and coefficients of variation were calculated using BMDP computer programs 1R, 6R, and 8D.[21] All data are expressed as mean ± SEM.

RESULTS

Body composition and $\dot{V}O_2$max. As compared with controls, the weight lifters had 35% higher relative and 45% greater absolute muscle mass ($P < 0.01$), whereas the relative contribution of fat to body weight was reduced by 45–50% ($P < 0.001$, Table 1). $\dot{V}O_2$max levels were comparable in the two groups. Runners had muscle mass similar to that in controls, whereas both the absolute and relative adipose tissue mass was 40–50% lower ($P < 0.01$) and $\dot{V}O_2$max 50% higher than in the controls ($P < 0.001$). As compared with the runners, the weight lifters had 34% higher relative and 64% greater absolute muscle mass and 30% lower $\dot{V}O_2$max levels ($P < 0.01$). The relative proportion of adipose tissue was virtually identical in the two groups.

Euglycemic clamp. The fasting insulin concentrations were similar in the weight lifters (7.6 ± 0.6 mU/L), runners (7.9 ± 1.0 mU/L), and controls (7.8 ± 1.1 mU/L). During the insulin infusion, the steady-state (20–120 min) plasma insulin levels were 85 ± 4 mU/L, 90 ± 5 mU/L, and 85 ± 7 mU/L, in the weight lifters, runners, and controls, respectively. The stability of the plasma insulin concentration during sustained hyperinsulinemia is indicated by the coefficients of variation, which were 8.6 ± 1.1%, 7.0 ± 0.9%, and 7.7 ± 1.5% in the

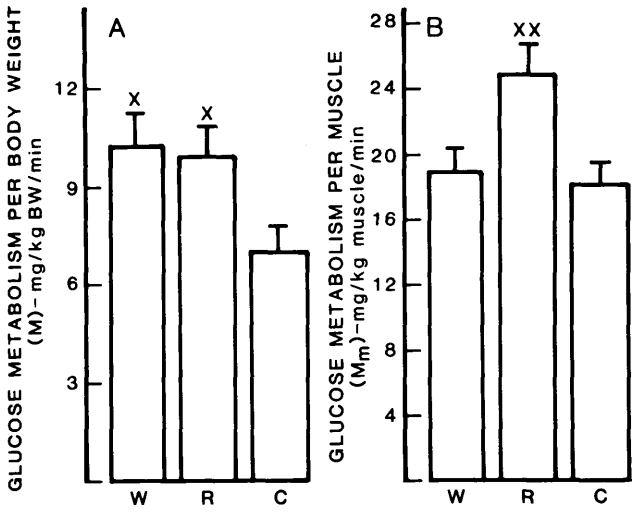

FIGURE 1. Glucose metabolism during the euglycemic clamp study expressed as mg/kg BW/min (A) or mg/kg muscle/min (B) in weight lifters (W), runners (R), and controls (C). Data are presented as mean ± SEM. $^{x}P < 0.05$ versus controls; $^{xx}P < 0.02$ versus controls.

three groups, respectively. The fasting plasma glucose concentrations in the weight lifters, runners, and controls were 94 ± 3 mg/dl, 88 ± 2 mg/dl, and 92 ± 2 mg/dl, respectively. During the period of hyperinsulinemia (20–120 min), the plasma glucose concentration was maintained at 90 ± 2 mg/dl, 87 ± 2 mg/dl, and 87 ± 2 mg/dl in the three groups, respectively. The coefficients of variation for plasma glucose concentrations during hyperinsulinemia were 6.9 ± 1.1%, 7.4 ± 0.7%, and 5.5 ± 0.8% in the weight lifters, runners, and controls, respectively.

The amount of glucose infused (M) to maintain euglycemia, as calculated per total BW, was virtually identical in the weight lifters (10.26 ± 1.02 mg/kg BW/min) and the runners (10.03 ± 0.86), and 40–45% higher than in the controls (7.10 ± 0.75 mg/kg BW/min, $P < 0.05$, Figure 1A). When the amount of glucose metabolized was calculated per body surface area (M_a), it was 45% higher in the weight lifters (410.8 ± 41.5 mg/m^2/min) than in the controls (286.1 ± 27.9 mg/m^2/min, $P < 0.05$). In the runners, M_a tended to be higher (369.8 ± 31.3) than in the controls ($0.05 < P < 0.1$). When glucose metabolism was calculated per muscle mass (M_m), only the runners (24.9 ± 1.9 mg/kg muscle/min) differed from the controls (18.3 ± 1.4 mg/kg muscle/min, $P < 0.02$, Figure 1B), whereas the value in weight lifters (19.0 ± 1.6 mg/kg muscle/min) was virtually identical to that in the controls.

Relationship between body composition and glucose metabolism. When simple correlations were calculated, M was directly proportional to % muscle ($r = 0.54$, $P < 0.01$, Figure 2), and inversely related to % fat ($r = -0.72$, $P < 0.001$, Figure 3). No relationship was observed between M and total BW ($r = 0.02$). When M was plotted against $\dot{V}O_2$max, a positive relationship was found when it was expressed per muscle mass (M_m) ($r = 0.61$, $P < 0.01$). No relationship was seen between $\dot{V}O_2$max and total M ($r = 0.30$, NS) or M_a ($r = 0.15$, NS). However, when only runners and controls with similar amounts of muscle mass were included, M was proportional to $\dot{V}O_2$max ($r = 0.52$, $P < 0.05$).

To evaluate more precisely the contribution of each of the three factors (% muscle, % fat, and $\dot{V}O_2$max) per se on M, we employed partial correlation coefficient analysis. When M was plotted against % muscle, the partial correlation was 0.415 ($P = 0.06$, NS), against % fat −0.33 (NS), and against $\dot{V}O_2$max 0.25 (NS). The combined effect of % muscle, % fat, and $\dot{V}O_2$max on M was calculated by using multiple linear regression analysis. The multivariate correlation coefficient between M versus % muscle, % fat, and $\dot{V}O_2$max altogether was 0.78 ($P < 0.0005$). The regression equation obtained for the predicted M was: M (mg/kg BW/min) = 0.697 + 0.155 · % muscle − 0.312 · % fat + 0.065 · $\dot{V}O_2$max (ml/kg/min).

DISCUSSION

In the current study, we selected the three groups of subjects in order to measure glucose metabolism in nonobese subjects with a wide range of different body compositions and maximal aerobic power, each of these being factors we thought might have an influence on body sensitivity to insulin. Muscle mass was determined by the use of muscle area of upper extremity,[16,17] and adipose tissue was measured from skinfold thickness,[18] since both of these methods are accurate for lean people.[22,23] In addition, to have the best possible accuracy, the same investigator performed all the body composition measurements. Weight lifters had a large muscle mass and a low amount of adipose tissue, whereas runners were characterized by enhanced $\dot{V}O_2$max, normal amount of muscle mass, but reduced adipose tissue as compared with controls.

The amount of glucose metabolized during euglycemic clamp is the sum of infused plus endogenously (by the liver) produced glucose. Although we did not measure hepatic glucose production, data from other laboratories indicate

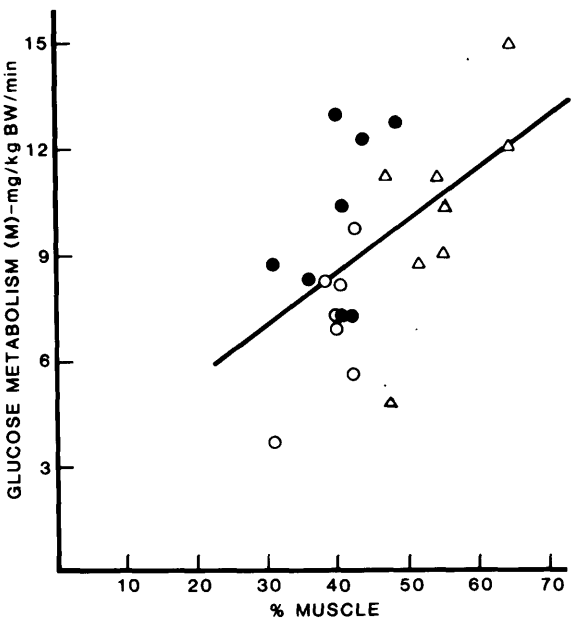

FIGURE 2. The relationship between the % muscle and the glucose metabolism in the weight lifters (△), runners (●), and controls (○). $r = 0.54$, $P < 0.01$.

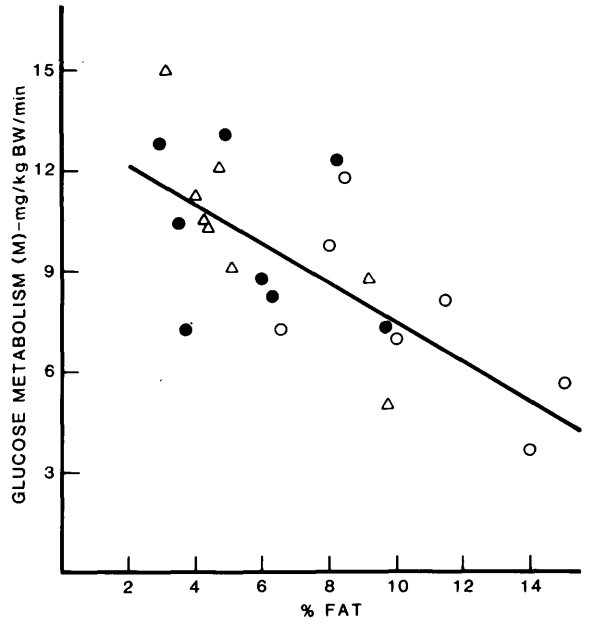

FIGURE 3. The relationship between the % fat and the glucose metabolism in the weight lifters (△), runners (●), and controls (○). r = −0.72, P < 0.001.

95–100% suppression of hepatic glucose production during a hyperinsulinemia comparable to our study.[24–26] Thus, any increase in the glucose infusion rate would reflect enhanced peripheral glucose uptake rather than increased hepatic suppression during a clamp study. Studies in untrained subjects with a direct calorimetry and hepatic and femoral venous catheterization show that during euglycemic hyperinsulinemia muscle tissue is responsible for 85% of the glucose disposal, in contrast to less than 5% taken up by the adipose tissue.[26] Thus, one would anticipate that M is proportional to the amount of muscle mass.

Our results demonstrate that insulin-mediated glucose disposal, expressed per total BW or per surface area, was 30–45% higher in weight lifters and runners as compared with controls (Figure 1A). Furthermore, a direct simple correlation was observed between M and % muscle (Figure 2). However, when the rate of glucose metabolism was expressed per kg of muscle tissue, it was similar in the weight lifters and controls and elevated only in the runners (Figure 1B). The data thus suggest that the elevated M value in the weight lifters may not reflect a change in muscle metabolism but simply the fact that with a large amount of glucose-consuming tissue present, the rate of glucose utilization is elevated.

Since the amount of muscle mass in the runners was similar to that in the controls, there should be factors other than muscle quantity to explain the difference in insulin sensitivity. At least two factors could be considered. First, in runners and controls, insulin sensitivity is shown to be proportional to $\dot{V}O_2$max.[27–29] This relationship was confirmed in the present study. Factors that may mediate the enhanced glucose uptake after training or weight loss are increased capillary supply in muscle tissue[30,31] and augmented insulin binding to receptors.[27,28] Second, the amount of adiposity may influence body sensitivity in the runners as well as in the others. This notion is supported by our observation of a negative correlation between M and % fat (Figure 3). The importance of adiposity is further suggested by the fact that obese subjects are insulin resistant, yet their absolute muscle mass can be normal or even increased.[32,33]

To evaluate the importance of each of the three factors on glucose metabolism, we calculated both the separate and combined effects of % muscle, % fat, and $\dot{V}O_2$max on insulin sensitivity. In this analysis, none of these factors alone correlated significantly with insulin sensitivity, although the relationship between M and % muscle was of borderline significance (P = 0.06). However, when the combined effect of these factors on M was calculated, a highly significant correlation was found (P < 0.0005). Thus, with the use of body composition and $\dot{V}O_2$max, one can fairly accurately predict the rate of glucose metabolism in healthy man.

Taken together, our findings have clinical implications in demonstrating that body composition as well as $\dot{V}O_2$max are important determinants of insulin sensitivity. Thus, one has to take into account not only total BW but also body composition and $\dot{V}O_2$max when insulin sensitivities in various groups of subjects are compared. Furthermore, our data raise the possibility that one factor contributing to decreased insulin sensitivity in obesity, the aged, or during physical inactivity is a change in body composition.

ACKNOWLEDGMENTS

The help of Sirkka-Liisa Karonen, Ph.D., for insulin determinations; Risto Elovainio, M.D., for the measurement of $\dot{V}O_2$max; Esa-Matti Tolppanen, M.D., for statistical analysis; and the skillful technical assistance of Anne Salo are acknowledged. We appreciate the advice of Ralph A. DeFronzo, M.D., in establishing the glucose clamp technique.

This study was supported by grants from the Finnish Ministry of Education, the Finnish Culture Foundation, and Nordisk Insulinfond (Gentofte, Denmark).

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