Skeletal Muscle Lipid Content and Insulin Resistance: Evidence for a Paradox in Endurance-Trained Athletes

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We examined the hypothesis that an excess accumulation of intramuscular lipid (IMCL) is associated with insulin resistance and that this may be mediated by the oxidative capacity of muscle. Nine sedentary lean (L) and 11 obese (O) subjects, 8 obese subjects with type 2 diabetes mellitus (D), and 9 lean, exercise-trained (T) subjects volunteered for this study. Insulin sensitivity (M) determined during a hyperinsulinemic (40 mU·m⁻²·min⁻¹) euglycemic clamp was greater (P < 0.01) in L and T, compared with O and D (9.45 ± 0.59 and 10.26 ± 0.78 vs. 5.31 ± 0.61 and 1.15 ± 0.83 mg·min⁻¹·kg fat free mass⁻¹, respectively). IMCL in percutaneous vastus lateralis biopsy specimens by quantitative image analysis of Oil Red O staining was approximately 2-fold higher in D than in L (3.04 ± 0.39 vs. 1.40 ± 0.28% area as lipid; P < 0.01). IMCL was also higher in T (2.36 ± 0.37), compared with L (P < 0.01). The oxidative capacity of muscle determined with succinate dehydrogenase staining of muscle fibers was higher in T, compared with L, O, and D (50.0 ± 4.4, 36.1 ± 4.4, 29.7 ± 3.8, and 33.4 ± 4.7 optical density units, respectively; P < 0.01). IMCL was negatively associated with M (r = −0.57, P < 0.05) when endurance-trained subjects were excluded from the analysis, and this association was independent of body mass index. However, the relationship between IMCL and M was not significant when trained individuals were included. There was a positive association between the oxidative capacity and M among nondiabetics (r = 0.37, P < 0.05). In summary, skeletal muscle of trained endurance athletes is markedly insulin sensitive and has a high oxidative capacity, despite having an elevated lipid content. In conclusion, the capacity for lipid oxidation may be an important mediator of the association between excess muscle lipid accumulation and insulin resistance. (J Clin Endocrinol Metab 86: 5755–5761, 2001)

Recent evidence suggests that an excess accumulation of skeletal muscle lipid is associated with insulin resistance in human obesity (1–6) and in type 2 diabetes mellitus (DM) (7, 8). Animal models of insulin resistance also lend support to this concept (9–11). Typically, muscle triglyceride (TG) concentrations have been measured using biochemical extraction methods in homogenates from either percutaneous biopsies or whole muscle (4, 5, 7, 8, 10). Thus, it is not certain whether the increased muscle TG concentrations were confounded by contamination from adipose tissue. Recent studies (1, 3, 6, 12, 13) using magnetic resonance spectroscopy (MRS) have also found that intramyocellular lipid is negatively associated with insulin sensitivity in vivo, although absolute concentrations of lipid using this methodology has yet to be quantified. Our group has recently demonstrated, using quantitative histochemistry, that the lipid contained within muscle fibers from obese subjects with type 2 DM was higher, compared with lean nondiabetics (14). Therefore, one hypothesis tested in the current study was that an excess accumulation of lipid within muscle fibers is associated with insulin resistance independent of obesity.

Insulin resistant skeletal muscle is characterized by lower oxidative capacity (15, 16) and lower postabsorptive rates of fatty acid oxidation (17). Elevated concentrations of lipid contained within skeletal muscle have also been linked to an impaired oxidative capacity of muscle (15) and lower rates of fatty acid oxidation by muscle (17). This raises the possibility that the association between lipid accumulation within muscle and insulin resistance is influenced by a lower capacity for the oxidation of lipid as an energy substrate.

Exercise training enhances insulin sensitivity (18–21) and the capacity for lipid oxidation (5, 22–24). Exercise training also increases fatty acid oxidation from intramuscular TG stores during exercise (25). However, the effect of exercise training on intramuscular TG is equivocal; some studies have demonstrated that training increases intramuscular TG (26, 27), and others have shown a decrease with exercise training (28). Accumulation of TG within skeletal muscle may not be invariably linked to insulin resistance. The possibility that endurance-trained athletes have an enhanced storage of intramuscular TG despite their high insulin sensitivity within muscle would contradict the apparent general association between increased intramuscular TG and insulin resistance. This serves as the basis for the intriguing hypothesis that the capacity for oxidative metabolism is an important mediator in the association between intramuscular lipid and insulin resistance.

Experimental Subjects

Nine lean and 8 obese volunteers with type 2 DM, 11 obese nondiabetics, and 9 endurance-trained athletes between the ages of 25 and 50 yr were recruited by public advertisement. Before participation, all potential research volunteers underwent a medical screening evaluation before participation. All volunteers were normotensive and had fasting TG and cholesterol levels less than 300 mg/dl without any antihypertensive or lipid-lowering medications. Women taking oral...
contraceptives were also excluded. Type 2 DM volunteers had been withdrawn from oral antidiabetic medications for at least 2 wk before this study, and none had received insulin. Type 2 DM patients were excluded if they had moderate to severe complications of DM such as retinopathy or peripheral neuropathy. None of the lean, obese nondiabetic individuals or those with type 2 DM were currently engaged in exercise training, and all but two were involved in competitive cycling. The study was approved by the University of Pittsburgh Institutional Review Board, and informed written consent was obtained from each volunteer.

**Materials and Methods**

**Muscle biopsies**

Subjects were instructed not to perform physical exercise 48 h before the muscle biopsy procedure to help prevent acute effects of exercise on muscle TG. Subjects were given a standard 10 kcal/kg meal consisting of 50% carbohydrate, 30% fat, and 20% protein the night before the biopsy and then fasted overnight.

Muscle biopsies were obtained from the middle region of the vastus lateralis muscle (15 cm above the patella) and approximately 2 cm away from the fascia by the percutaneous needle biopsy technique as described by Evans et al. (29). Muscle specimens were trimmed, mounted, and frozen in isopentane cooled at −160°C by liquid nitrogen and stored at −80°C for histochemical analysis.

**Histochemical analysis**

Histochemical analyses were performed on light microscopic micrographs of 8-μm-thick transverse cryostat sections at −29°C (Micron HM505E, Walldorf, Germany). Initial sections from each frozen muscle block were inspected without stain to ensure that proper cross-sectional cuts were being obtained; if not, then the orientation was adjusted and this process repeated until good cross-sectional orientation was obtained. Muscle sectioning, staining, and image analysis were done in a blinded manner with respect to group.

Lipid staining was done using the Oil Red O soluble dye, which stains neutral lipid (mainly TGs) with an orange-red tint (30) (Fig. 1). The intramuscular lipid (IMCL) content was determined as previously described (14). Briefly, an Olympus Corp. light microscope (Provis, Tokyo, Japan) was used to examine the stained muscle sections, using a 40× oil immersion objective and bright field settings. Images were digitally captured using a CCD camera (Sony, Tokyo, Japan). Contiguous fields of view within the biopsy section that were free from artifact were analyzed for lipid content; quantitative image analysis was then carried out on at least 80 fibers, or approximately 10 contiguous fibers per field.

Images from each file were saved as gray-scale images (TIFF file format), and the digitized data were then analyzed with the freeware NIH Image software (rsb.info.nih.gov/nih-image/). Oil Red staining was quantified as the area occupied by lipid staining: LAI = (total area occupied by lipid droplets of muscle fiber)/100/(total cross-sectional area of a muscle fiber). The LAI was calculated for each of eight fields within the section and a mean LAI was then calculated for each volunteer. A control section treated with acetone and subsequently stained revealed no visible staining and thus no background staining was observed.

Oxidative capacity of muscle was determined with succinate dehydrogenase (SDH) staining (31). Quantification of SDH staining was performed using image analysis of staining intensity, a method that has been verified with biochemical determination of SDH activity in muscle (32, 33). As negative control slides for this reaction, to assess background staining, sections were incubated in media without the enzyme substrate succinate. The proportion of type 1, 2a, and 2b muscle fibers was also determined on cryosections containing at least 300 fibers by ATPase staining (34).

**Insulin sensitivity**

Insulin sensitivity was determined using the hyperinsulinemic (40 mU·m−2·min−1), euglycemic clamp method as previously described (2). Subjects were instructed to avoid strenuous activity for 2 d preceding these studies. On the day before measurement of insulin sensitivity, subjects were admitted to the University of Pittsburgh General Clinical Research Center. That evening they received a standard dinner (10 kcal/kg; 50% carbohydrate, 30% fat, 20% protein) and then fasted until the morning of the study. After obtaining basal blood samples, a primed constant infusion of [6, 6-2H2] glucose (0.22 μmol·kg−1·min−1, 17.6 μmol·kg−1·prime) 99% enriched (Isotech, Inc., Miamisburg, OH) was started with a calibrated syringe pump (Harvard Apparatus, Natick, MA), allowing 2 h for isotopic equilibration before the initiation of the insulin infusion in only subjects with type 2 DM. Euglycemia was maintained using an adjustable infusion of 20% dextrose, to which [6, 6-2H2] glucose was added to maintain stable plasma glucose enrichment (35). Plasma glucose was determined at 5-min intervals during the 4-h clamp. Blood samples for measurement of [6, 6-2H2] glucose enrichment were collected every 10 min during the final 40 min of insulin infusion.

**Analyses**

Plasma glucose was measured using an automated glucose oxidase reaction (2300 glucose analyzer, YSI, Inc., Yellow Springs, OH). Enrichment of plasma [6, 6-2H2] glucose enrichment was determined by gas chromatography-mass spectrometry (HP 5971 MS, 5890 Series 2 GC; Hewlett Packard, Palo Alto, CA) analysis of the glucose penta-acetate derivatives, selectively monitoring ions at mass-to-charge 200 and 202.

**Calculations.** Rate of plasma glucose appearance and utilization were calculated using the Steele equations (36), as modified for variable rate glucose infusions, which contain isotope (35).

**Statistical analysis.** Data are presented as mean ± sem, unless otherwise indicated. Group differences in IMCL, muscle oxidative staining, and insulin sensitivity were assessed with one-way ANOVA, using the Bonferroni correction for specific group comparisons. The relationships between insulin sensitivity and intramuscular lipid and muscle oxidative staining were determined with bivariate regression analysis. Stepwise multivariate regression analysis was used to determine these associations after adjusting for total adiposity. All
statistics were performed using JMP version 3.1.6 for the Macintosh (SAS Institute, Inc., Cary, NC).

Results

Subject clinical characteristics

Lean and obese volunteers and obese subjects with type 2 DM were considered sedentary from their recent physical activity levels; none of these individuals were participating in regular exercise. The endurance-trained subjects were currently participating in at least 5 d/wk of aerobic exercise training. Moreover, the athletes had a relatively high aerobic capacity as evidenced by their maximal oxygen uptake of 61.0 ± 5.4 ml/kg per min, determined in another study protocol.

The general body composition characteristics of these subjects are described in Table 1. Obese subjects with type 2 diabetes were older than nondiabetics. Per study design, lean sedentary and trained subjects had a lower body mass index than either the obese or obese type 2 DM groups. Accordingly, their total and proportion of body fat were also lower as determined by DXA, model DPX-L (Lunar Corp., Madison, WI) using software version 1.3Z. Fasting plasma glucose was higher (P < 0.05) in the obese subjects with type 2 DM, compared with nondiabetics, who had similar fasting plasma glucose values (Table 2). Serum TG concentrations were significantly lower (P < 0.05) in the trained group (Table 2).

Insulin sensitivity

Values for insulin sensitivity are represented relative to fat free mass. Lean subjects were nearly twice as insulin sensitive, compared with obese subjects (P < 0.05; Fig. 2). Expectedly, those with type 2 DM were markedly insulin resistant, compared with those without diabetes (P < 0.05). Insulin sensitivity was similar in lean sedentary subjects and lean endurance-trained subjects.

Skeletal muscle lipid and oxidative capacity

The content of IMCL was approximately 2-fold higher in type 2 DM, compared with lean sedentary subjects (P < 0.05; Fig. 3). Trained subjects also had higher IMCL than the lean untrained subjects (P < 0.05), and indeed these values for trained subjects were similar to that of diabetic muscle. The oxidative capacity of muscle, determined by the SDH staining intensity, was 65% higher in trained muscle, compared with the sedentary obese group and 50% higher than those with type 2 DM (P < 0.05 for both; Fig. 4). The oxidative capacity also tended to be higher in trained subjects, compared with the lean sedentary group, but this difference was not significant. The oxidative capacities of lean, obese, and obese type 2 DM sedentary subjects were not significantly different. Interestingly, muscle fiber type was not different among the four groups. The proportion of type 1 fibers was 40 ± 8, 35 ± 4, 39 ± 7, and 44 ± 4 for lean, obese, obese type 2 DM, and trained subjects, respectively. The proportion of type 2a and 2b fibers was also not different among groups.

Association of muscle lipid and oxidative capacity with insulin resistance

Among sedentary subjects, there was an inverse association between the amount of lipid contained within muscle fibers (IMCL) and insulin sensitivity (Fig. 5), in which IMCL accounted for 32% of the variance in insulin sensitivity. This relationship remained significant (P < 0.05) when obese individuals with type 2 DM omitted from the analysis, though the observed variance was reduced to 19%. Moreover, stepwise multivariate regression revealed that the association between IMCL and insulin resistance was independent of total adiposity and age. However, the negative association between IMCL and insulin sensitivity was observed only when the trained subjects were excluded from the analysis; there was no association (r² = 0.03) when exercise-trained individuals were included.

There was a positive association between the oxidative capacity of muscle determined with SDH staining and insulin sensitivity (Fig. 6), but only when the obese subjects with type 2 diabetes were omitted from the analysis. The profound insulin resistance in the diabetics likely contributed to our inability to detect this association with these subjects included. In fact, three of the obese subjects with diabetes had no measurable insulin-stimulated glucose disposal. Nevertheless, this positive correlation between SDH staining and insulin sensitivity is consistent with the higher oxidative capacity and higher insulin sensitivity in the trained groups, compared with the sedentary groups.

Discussion

A primary finding of the present study was that the lipid contained within muscle fibers of sedentary individuals was inversely associated with insulin resistance. However, individuals engaged in regular exercise training had higher mus-

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**TABLE 1. Subject physical characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
<th>Type 2 DM</th>
<th>Trained</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>38.7 ± 3.3</td>
<td>40.8 ± 2.5</td>
<td>51.0 ± 1.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.3 ± 2.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1 ± 1.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>102.7 ± 5.5</td>
<td>96.5 ± 0.7</td>
<td>76.0 ± 3.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>25.2 ± 0.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.9 ± 1.0</td>
<td>30.9 ± 1.2</td>
<td>25.3 ± 0.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>23.7 ± 3.6</td>
<td>32.8 ± 2.4</td>
<td>32.5 ± 2.7</td>
<td>14.5 ± 1.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>57.9 ± 2.4</td>
<td>69.5 ± 5.8</td>
<td>65.1 ± 2.2</td>
<td>64.9 ± 2.9</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE of the mean. P values are given below for specific comparisons.

<sup>a</sup> Different from all other groups within gender, P < 0.01.

<sup>b</sup> Different from obese and type 2 DM, P < 0.01. The trained women (n = 1) were not included in the within-gender analysis. BMI, Body mass index.
cle fiber lipid content despite being markedly insulin sensitive. The higher oxidative capacity of skeletal muscle in these trained athletes provides a likely intermediary in the association between muscle lipid content and insulin resistance. By examining the muscle lipid content, oxidative capacity, and insulin sensitivity in trained and sedentary individuals, we have identified potential mediators governing the association between skeletal muscle lipid and insulin resistance of obesity and type 2 DM.

Skeletal muscle lipid within muscle fibers was directly ascertained with quantitative histochemical analysis of biopsy specimens, reflecting true intracellular concentration of lipid. Because of inherent limitations of prior methods, prior studies have relied on certain assumptions in their measurements of intramuscular TG concentrations. Quantifying intramuscular TG in human biopsy samples has typically involved the biochemical extraction of TG, possibly resulting in the inadvertent contamination of fat and connective tissue within the sample (4, 5, 7, 8, 10). Proton MRS studies of human muscle performed by several independent groups have recently differentiated extra- and intramyocellular lipid (IMCL) and have observed negative associations between IMCL and insulin sensitivity (1, 3, 6, 12, 13). Although MRS represents a novel noninvasive method to determine relative IMCL content in vivo, quantification of actual IMCL concentrations using MRS remains problematic. Nevertheless, the prior observed associations between IMCL and insulin resistance should not be discounted. On the contrary, our findings confirm those of these previous studies demonstrating that increased lipid stored within muscle fibers is indeed associated with insulin resistance.

Despite their expectedly higher insulin sensitivity, compared with obese subjects and with those with type 2 DM, the IMCL content in the trained subjects in this study was similar to individuals with type 2 DM. Moreover, the observed association between IMCL and insulin resistance disappeared when trained subjects were included in the analysis. In previous studies observing associations between IMCL and insulin resistance, the influence of physical fitness or physical activity was not directly assessed (1, 3–6, 12, 13). Thus, this study represents the first examination of the potential influence of physical training on the association between IMCL and insulin resistance. Interestingly, insulin sensitivity in these athletes was not greater, compared with lean sedentary men and women. This finding is supported by other studies finding only modest or no improvements in insulin sensitivity with exercise training when the effects of weight loss (21) and the last exercise session (21, 37) are accounted for.

Although their insulin sensitivity was similar, endurance-trained athletes had nearly 2-fold higher amounts of lipid stored within their muscle fibers, compared with their lean, type 2 DM.

### Table 2. Subject clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
<th>Type 2 DM</th>
<th>Trained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mM)</td>
<td>5.02 ± 0.16</td>
<td>4.94 ± 0.15</td>
<td>9.54 ± 1.23*</td>
<td>4.65 ± 0.11</td>
</tr>
<tr>
<td>Serum cholesterol (g/dl)</td>
<td>182 ± 13</td>
<td>209 ± 18</td>
<td>220 ± 16</td>
<td>171 ± 18</td>
</tr>
<tr>
<td>Serum TG (g/dl)</td>
<td>124 ± 35</td>
<td>147 ± 19</td>
<td>157 ± 22</td>
<td>87 ± 19*</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE of the mean; *P values are given below for specific comparisons.

* Different from all other groups, *P < 0.01.

![Fig. 2. Insulin sensitivity in lean and obese subjects, obese subjects with type 2 DM, and exercise-trained subjects. *P < 0.05 vs. obese and type 2 DM groups; **P < 0.05 vs. type 2 DM group only. Results are mean ± SE.](image)

![Fig. 3. IMCL content in lean and obese subjects, obese subjects with type 2 DM, and exercise-trained subjects. *P < 0.05 vs. lean and obese groups; **P < 0.05 vs. lean group only. Results are mean ± SE.](image)
This finding is in accord with Hoppeker et al. (26), who observed that the volume of lipid droplets on electron micrographs was higher in trained subjects. However, IMCL quantification in that study was confined to the ultrastructure scale, which limited the scope of quantification. Boesch and Kreis (38) found in using MRS that IMCL was higher in one trained athlete, compared with other sedentary but otherwise healthy subjects. The effects of training on IMCL have not been clear, with some studies reporting higher concentrations of IMCL after training (27, 39) and others reporting decreases (28). These disparate results are not entirely surprising given the relatively small number of studies and the relatively high interbiopsy variability in the measure of IMCL (40). With relatively short-term training studies, it is conceivable that the specific adaptation to enhance TG storage had not yet occurred during the course of the study. There also remains the possibility that the subcellular localization of lipid within muscle may impact upon the association with insulin action.

The higher IMCL content in these trained athletes raises the possibility that IMCL is merely a surrogate for other factors in muscle that may directly affect insulin-stimulated glucose metabolism. Thompson and Cooney (41) recently reported that long chain fatty acyl CoA in skeletal muscle may induce insulin resistance by inhibiting hexokinase activity. Other reports suggest that long chain CoA and diacylglycerol, metabolites of IMCL metabolism, act on insulin signaling pathways in muscle (42, 43). Thus, no direct effect of muscle TG on insulin-stimulated glucose metabolism has been defined. Moreover, periodic turnover of IMCL and its associated metabolites with regular exercise may limit their negative influence on insulin signaling. Further studies are needed to specifically examine the effects of training on these lipid metabolites within muscle and, in general, how they may play a role in insulin resistance.

Alternative mechanisms may help elucidate the reasons that these trained athletes had high IMCL concomitant with their high insulin sensitivity. Factors governing the enhanced insulin sensitivity in muscle with exercise training such as
increased GLUT 4 content (44, 45) and skeletal muscle blood flow (44) may override the negative consequences of IMCL on insulin-stimulated glucose metabolism. Thus, it is likely that the upregulation of these intermediates in the trained subjects at least partially modulated any deleterious effect of increased IMCL on insulin sensitivity. In addition, we addressed the role of the oxidative capacity of muscle as a mediator of insulin sensitivity.

The oxidative capacity was higher in trained subjects in accord with prior studies (22, 23, 46, 47). This, together with the high IMCL and insulin sensitivity in these subjects, suggests that the capacity for IMCL oxidation is an important intermediary of insulin resistance. A higher oxidative capacity within muscle reflects their increased mitochondria content and enhanced capacity for lipid oxidation. Including the trained subjects in the analysis, a lower oxidative capacity was associated with insulin resistance. This is in agreement with prior studies demonstrating that skeletal muscle from insulin-resistant and obese subjects is characterized by lower oxidative capacity (15, 17) and lower fasting rates of fatty acid oxidation (17, 48, 49). As a storage depot of fatty acids, IMCLs are changeable. During moderate exercise, fatty acids from the hydrolysis of IMCL are capable of contributing a substantial portion of the energy required for oxidative metabolism (25, 50, 51). Perhaps the periodic utilization of this energy source should be considered as an important factor mediating the association between IMCL and insulin resistance. Little, if any, fatty acids from IMCL are oxidized during resting conditions (52). The deficient utilization and subsequent accumulation of IMCL in sedentary subjects may confer insulin resistance, whereas the periodic utilization of this energy substrate during regular exercise may overcome this consequence of IMCL accrual.

Recent studies in mice overexpressing uncoupling protein also provide support for the role of an increased capacity for fatty acid oxidation to mediate the potential negative influence of IMCL on insulin-stimulated glucose metabolism (53). IMCL in mice overexpressing uncoupling protein was increased despite an increase in energy expenditure, GLUT 4 content, hexokinase activity within muscle, and a decrease in overall adiposity (53). Thus, in many respects, this transgenic animal model mimics the situation observed in skeletal muscle of endurance-trained athletes in which IMCLs are higher than in sedentary individuals with similar insulin sensitivity. Lipoprotein lipase (LPL) in skeletal muscle also plays a direct role in IMCL accretion (54), and exercise increases muscle LPL (55). Thus, it is likely that the induction of muscle LPL following exercise helps to replenish IMCL following exercise (56, 57). More studies are required to demonstrate whether an elevated muscle LPL in trained athletes influences their elevated IMCL content.

In summary, the association between intramuscular lipid content and insulin resistance may be influenced by the oxidative capacity of skeletal muscle. The higher concentrations of lipid stored within muscle fibers, in conjunction with a higher oxidative capacity and insulin sensitivity of individuals participating in regular exercise, provide support for this concept. It is likely that intramuscular lipid content alone may not confer insulin resistance but rather may act as a surrogate for other potentially detrimental lipid metabolites.

Future studies should examine the effects of exercise training on the interactions between fatty acid metabolism and insulin resistance of obesity and type 2 DM.

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