Cessation of physical exercise changes metabolism and modifies the adipocyte cellularity of the periepididymal white adipose tissue in rats

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WHITE ADIPOSE TISSUE (WAT) is the largest energy reservoir of the body. In addition to being a major source of energy, it was observed nearly 2 decades ago that WAT is also an important source of biologically active substances. Consequently, WAT was recognized as an endocrine organ that plays an active role in the regulation of energy metabolism (1, 13).

Because WAT is an important metabolic center, it is unsurprising that it is involved in adaptations to both endogenous and exogenous events. Physical exercise is one of the exogenous factors able to cause adaptive changes in WAT. The overall effect of physical exercise is to increase the rate of mobility and the oxidation of triacylglycerols (TAG), causing a decrease in fat mass and, consequently, weight loss by inducing a negative energy balance (6, 17).

The principle of reversibility (principle of adaptation) is inherent to the benefits of physical training and states that when physical training is suspended or decreased (physical detraining), body systems readjust based on this decrease until the complete cessation of exercise returns the individual to a sedentary condition (25).

The effects of physical detraining on striated muscles are well known. Highly trained distance runners showed decreased capillary density (capillaries per mm²) in muscle tissue after 15 days of detraining (34). Furthermore, it is known that after 21 days of detraining, maximum cardiac output decreases by ~26%, from 20 l/min to 14.8 l/min (9). Recently, a significant reduction in the muscle strength of older individuals after a short detraining period was observed (23). Physical detraining for 12 wk resulted in a significant reduction (17%) in strength resistance and a reduction (19%) in the rate of fatigue. In addition, intramuscular fat increased by 14% compared with the values observed before the cessation of training (31). The readjustments experienced by the body as a result of physical detraining also affect the hemoglobin mass (Hbmass). After 30 days of detraining, triathletes showed a decrease in Hbmass and maximal oxygen uptake (V̇O₂max), followed by an increase in body mass (11). Levels of both testosterone and free testosterone increased with physical exercise and returned to baseline levels after 4 wk of detraining (23).

Physical detraining affects several organs and body systems, but its influence on adipose tissue remains relatively unexplored. There is a positive correlation between physical detraining and both increases in visceral fat mass and cardiac risk factors (e.g., dyslipidemia) in children with obesity (14). Another study observed an increase in retroperitoneal, urogenital, and mesenteric fat mass in Sprague-Dawley female rats trained for 8 wk with treadmill exercise and untrained for 4 wk, with or without a high-fat diet (41).

Although the effects of physical exercise on adipose tissue metabolism are known, other possible implications remain unex-
plored, such as the influence of training on adipose tissue cellularity. In addition, the readjustments that occur in WAT during the detraining process have been less studied.

MATERIAL AND METHODS

Animals and Training Schedule

Male Wistar rats (45 days old, weight 200 g) from the Animal Resources Center of the Institute of Biomedical Sciences of the University of São Paulo were used in the experiments. The animals were divided into three groups (10 animals per group). 1) group T, trained for 12 wk; 2) group D, trained for 8 wk and untrained for the remaining 4 wk; and 3) group S, sedentary. The rats were housed in collective cages with free access to water and food (balanced cholw pellet diet, Nuvilab CR1, Nuvital SA, Colombo, Brazil) and kept on an inverted 12:12-h light/dark cycle (lights on at 6:00 p.m.). Body weight was measured weekly. Rats were initially preselected for their ability to walk on a treadmill (Inbramed K3000, 4–5 sessions at 0.3–0.5 km/h, 0% grade, and 10 min/day) and then randomly assigned to the T (Trained) or S (Sedentary) group. The training protocol was based on the procedures described by Negrao et al. (26) and adapted to our laboratory conditions. The exercise was progressive, with increases in intensity determined by a combination of velocity (0% grade) and time. The exercise was performed 5 days/wk for 12 wk and began at 0.3 km/h for 10–15 min/day, reaching 0.5 km/h and 30 min/day by week 1. The training intensity was gradually increased to 60 min/day (by week 3) at 1.0 km/h (by week 7), a schedule that was continued until the end of the experiment. The training protocol resulted in the rats reaching 50–60% of maximal race capacity, as determined in all of the rats before the 12-wk period and again every 2 wk to adjust the workload. The animals were killed 48 h after the last training session. Prior to death the animals were fasted for 12 h. All animals were preanesthetized with thiopental sodium (50 μg/g body wt) and decapitated. The Ethical Committee for Animal Research of the Institute of Biomedical Sciences of the University of Sao Paulo approved all of the experimental procedures.

Determination of the Citrate Synthase Activity in the Soleus Muscle

The maximum activity of citrate synthase was determined as previously described (2). Samples (100 μl) of soleus muscle were excised and homogenized (two bouts, 10 s each, at maximum speed, Polytorn PT 3100, Kinematica, Littau-Lucerne, Switzerland) in 1 ml of extraction buffer (50 mM Tris/HCl and 1 mM EDTA, pH 7.4) and centrifuged (3,800 g, 30 s, 4°C). The supernatant was analyzed spectrophotometrically (412 nm) for the maximum activity of citrate synthase. The protein content was quantified using bicinchoninic acid reagents. The maximal enzyme activity was expressed as nanomoles per minute per milligram of protein.

Determination of the Activities of Lipogenic Enzymes (FAS, MALIC, and G6PDH)

Samples of the PE adipose tissue were homogenized in extraction buffer (1:1 ratio) containing 50 mM Tris/HCl, 1 mM EDTA, centrifuged (12,000 g, 30 s, 4°C) and 50 μl of infranatant were used to determine the enzyme activities of glucose-6-phosphate dehydrogenase (G6PDH), malic enzyme, and fatty acid synthase (FAS) in appropriate assay buffers according to protocols described elsewhere (6, 5, and 21, respectively).

Biochemical and Hormonal Measurements in Plasma

Nonesterified fatty acids (NEFA - Wako NEFA HR2), triacylglycerol (TAG - Bioclin K005), and total cholesterol (TC - Labtest 76-2) and cholesterol fractions (HDL-C, LDL-C Labtest 98-80) were determined using enzymatic methods with commercial kits. Insulin (RI-13K Linco Research,), leptin (RL-83K Linco Research,), and testoster-
group). The analysis of these results was performed using the Sigma ScanPro4 program.

Analysis of Chromatin Condensation Using Fluorescence Microscopy

This technique was used to determine the degree of cell apoptosis. The analysis was performed using a fluorescence microscope the expression of adipocyte-specific genes (30). The adipocytes in the sample (1 g of tissue) were isolated and resuspended in 20 μL of Hoechst 33342 (Molecular Probes) at 0.01 mg/ml in saline (NaCl 0.9%). After 10 min of incubation in the dark, 10 μL of sample was transferred to a glass slide and viewed with a fluorescence microscope with a 365/80 nm filter. This stain distinguishes nuclei with condensed chromatin in apoptosis from those with uncondensed chromatin in viable cells. The cells were analyzed using the program KS 300 (Carl Zeiss Vision).

Measurement of PPARγ, β3M, PREF1, and Adiponectin Gene Expression in the Stromal-Vascular Cell Fraction

RNA extraction. PE fat samples (1 g) were collected and subjected to digestion by collagenase to isolate the adipocytes. After digestion, the samples were subjected to centrifugation at 450 × g for 5 min. The pellet, which contained preadipocytes and newly differentiated adipocytes, macrophages, fibroblasts, and other cells, was collected.

Total RNA was extracted from the WAT in a guanidine isothiocyanate-based TRIzol solution according to the manufacturer’s specifications (8) and quantified spectrophotometrically at 260 nm. Superscript II RT was used to reverse transcribe 5 μg of total RNA isolated using an oligo-(dT)10 primer in a total reaction volume of 20 μL.

Real-time PCR. One microliter of cDNA was added to 12.5 μL of Platinum Sybr Green PCR SuperMix-UDG (Invitrogen), 9.5 μL of DEPC H2O, 1 μL of sense primer, and 1 μL of antisense primer (Table 1). The PCR reaction was evaluated using a Rotor Gene 6000 (Corbett Research, Mortlake, Australia). The gene expression analysis was normalized by comparison against B2M gene expression (constitutive). The relative amount of each target gene was analyzed using the comparative Ct (cycle threshold) method proposed by Livak and Schmittgen (22). The Ct value is the estimated number of cycles during which the emitted fluorescence signal is significantly above baseline levels.

Table 1. Sequences of primers used for gene expression studies

<table>
<thead>
<tr>
<th>Genes</th>
<th>Sense</th>
<th>Antisense</th>
<th>Hybridization Temperature, °C</th>
<th>Fragment Size, bp</th>
<th>Number of Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2M</td>
<td>5′-CAAGAAGGTCGAGGTGGCCGTGC3′</td>
<td>5′-CAGAGCGGATGCTCCAGGAGTC3′</td>
<td>56</td>
<td>290</td>
<td>40</td>
</tr>
<tr>
<td>PPARγ</td>
<td>5′-GTTGCTACCCGCTGGGGGATG3′</td>
<td>5′-CTGGAGCAGGAGAGAGGAGGCTG3′</td>
<td>56</td>
<td>168</td>
<td>40</td>
</tr>
<tr>
<td>AdipoQ</td>
<td>5′-ATGTCGCTAAGTGAAAGAGAACTGGGAG3′</td>
<td>5′-CTCTTAGGAGAGAGAGGAGGCTG3′</td>
<td>58</td>
<td>118</td>
<td>40</td>
</tr>
<tr>
<td>PREF1</td>
<td>5′-AAAGCGTGAGGAGGGAATTG3′</td>
<td>5′-CTGCGAGGACAGCATGATGAT3′</td>
<td>57.5</td>
<td>185</td>
<td>40</td>
</tr>
</tbody>
</table>

Statistical Analysis

All analyses were performed in a blinded fashion. The means ± SE of the individual data from each group were obtained and analyzed using a one-way ANOVA. Newman-Keuls posttest analyses were performed for comparisons between groups. The upper limit of significance for rejection of the null hypothesis was established at 5% (P < 0.05).

RESULTS

Efficacy of Chronic Exercise Training as Determined by the Maximal Activity of the Citrate Synthase Enzyme in Soleus Muscle

The maximal enzyme activity after 12 wk of exercise training significantly increased by ~20% in group T when compared with groups S and D (Fig. 1), indicating that the protocol used was effective in producing aerobic adaptations (possibly by inducing an increase in mitochondrial biogenesis). In summary, exercise training produced an adaptation, and detraining reversed this adaptation.

Effect on Body Weight

Table 2 shows the effects of physical training and detraining on the body weight of animals. During the first 8 wk, there were only two groups: S and T. After the 8th wk, some animals from group T discontinued the training (detraining), becoming group D. The animals from group T showed lower weight gain by the end of 12 wk when compared with the other groups. Detrained animals (D) fully recovered from the weight gain by the end of 12 wk when compared with the other groups. The body weight of the animals after 8 wk of training (13-wk-old animals) was already significantly lower than the weight of the sedentary animals. Therefore, the proposed training was very efficient at controlling the weight gain that naturally occurs during puberty, when growth is accelerated.

![Fig. 1. Citrate synthase activity. Effect of chronic aerobic exercise training and detraining on the maximum activity of the citrate synthase enzyme in the soleus muscle of rats after 12 wk of training (n = 10, *P < 0.05 T vs. S and D).](image_url)

Table 2. Body weight, body weight gain, and peripapillary fat pad weight

<table>
<thead>
<tr>
<th></th>
<th>Sedentary (n = 10)</th>
<th>Trained (n = 10)</th>
<th>Detrained (n = 10)</th>
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</thead>
<tbody>
<tr>
<td>Initial weight, g</td>
<td>202 ± 4.56</td>
<td>195.78 ± 3.53</td>
<td></td>
</tr>
<tr>
<td>Weight gain first 8 wk, g</td>
<td>114 ± 8.27</td>
<td>89.11 ± 5.406*</td>
<td></td>
</tr>
<tr>
<td>Weight after 8 wk, g</td>
<td>344.8 ± 8.85</td>
<td>314.22 ± 7.11*</td>
<td></td>
</tr>
<tr>
<td>Weight gain last 4 wk, g</td>
<td>30 ± 4.24</td>
<td>26 ± 4.4</td>
<td>46 ± 4.05*</td>
</tr>
<tr>
<td>Final weight, g</td>
<td>379.6 ± 10.09</td>
<td>326.5 ± 7.14*</td>
<td>384 ± 13.08</td>
</tr>
<tr>
<td>PE fat weight, g</td>
<td>5.18 ± 0.22</td>
<td>4.21 ± 0.20*</td>
<td>5.03 ± 0.24</td>
</tr>
</tbody>
</table>

Data are means ± SE. *P < 0.05 in relation to the other groups, n = 10.

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ally, the body weight gain of the group D animals was much higher than that of the other groups during the last 4 wk.

**Plasma Insulin, Leptin, and Testosterone Levels**

These results are shown in Table 3. Significant differences were only observed in leptin levels, and the leptin levels were significantly lower in group T than in groups S and D. Therefore the body weight regain resulting from detraining was followed by a significant increase in leptin levels, which is an important marker of the energy reserves of an animal.

**NEFA, Triacylglycerol, Total Cholesterol, LDL-C, and HDL-C**

Table 3 shows the results related to circulating lipids. We observed that both the total cholesterol (c) and triacylglycerol(TAG) were significantly reduced in the animals from group T compared with the animals from group S. However, HDL-C levels were significantly lower in the animals from group D compared with the animals from group S. Serum levels of LDL cholesterol and NEFA were similar between the studied groups.

**Determination of Adipocyte Size**

Figure 2 shows significant differences in the cross-sectional areas of PE adipocytes among groups S, T, and D. As noted, the adipocytes from the rats in group T (1,945.7 ± 45.6 µm²) were smaller than the adipocytes from the rats in group S (2,492.4 ± 49.08 µm²), which were smaller than the adipocytes from the rats in group D (3,474 ± 68.8 µm²). Therefore the weight regain of animals from group D was followed by the recovery of PE fat mass and a more pronounced hypertrophy of their adipocytes.

**Metabolic Capabilities of Adipocytes Isolated From Periepididymal Fat Pad**

**Incorporation of D-[U-14C]-glucose into lipids.** Figure 3, A (basal) and B (maximal), shows the results. Clearly, the ability of adipocytes to incorporate glucose into lipids is more pronounced in detrained animals than in trained animals. There was no significant difference between groups S and T. In group D the body weight regain and the subsequent recovery of PE fat mass was also associated with an increased ability of the adipocytes to incorporate glucose into lipids.

**Incorporation of [U-14C] glucose into the fatty acid residue of triacylglycerols.** Once a labeled glucose molecule enters a fat cell, it can follow various paths: 1) mitochondrial oxidation,
generating energy for the resynthesis of adenosine triphosphate (ATP); or 2) incorporation into TAG. In the latter scenario, glucose can be incorporated into the glycerol residue and/or the fatty acid residue. Figure 3, C (basal) and D (maximal), shows the incorporation of labeled glucose into the fatty acid. We observed that exercise training reduces the incorporation of glucose into the fatty acid residue of the TAG molecule and that detraining completely reverses this change, returning the amount incorporated to the level of the sedentary state.

Incorporation of $^{14}$C-acetate into the fatty acid residue of triacylglycerols. Acetate has only two metabolic pathways inside the adipocyte: either its complete oxidation or its incorporation during the synthesis of fatty acids. This test aimed to observe the de novo lipogenesis (DNL) resulting from the incorporation of acetate, which is not a lipid substrate, into fatty acids. Figure 3E shows these results. In Fig. 3E we also see that the lipogenic capacity of the adipocytes of the group D rats was higher than that of the adipocytes of the T rats.

Lipolysis in Isolated Adipocytes

The lipolytic capacity of adipocytes from the trained animals stimulated by isoproterenol (Fig. 3G) was smaller than that of the sedentary animals. Detraining induced a full recovery of the maximum lipolytic capacity. The basal lipolysis (Fig. 3F) was similar between the groups.

Study of the Maximum Activity of the Enzymes Involved in Fatty Acid Synthesis: FAS, Malic Enzyme, and G6PDH

Analysis of the maximum activity of the enzymes involved in TAG synthesis revealed that physical detraining restored the lipogenic activity that had been reduced by physical training (Fig. 4). Figure 4A shows that physical detraining highly increased malic enzyme activity.

Study of Adipocyte Cellularity

Real-time PCR. The vascular stroma of the PE adipose tissue was analyzed to investigate possible differences in the number of preadipocytes and recently differentiated adipocytes and the possible association of these findings with increases in fat mass (Fig. 5). The PPAR gamma gene expression was studied using real-time PCR (Fig. 5A). Physical training significantly increased PPAR gamma expression, and detraining did not reverse this result. Figure 5B shows the expression of the
PREF-1 gene, used as a marker of preadipocyte cells and the gene expression of which was significantly increased by physical training relative to the sedentary group. Figure 5C shows that the expression of the adiponectin gene (expressed in differentiated adipocytes but not in preadipocytes) significantly increased in group D relative to the other groups, suggesting that there is a greater population of recently differentiated adipocytes in the vascular stroma of detrained rats.

Analysis of chromatin condensation using fluorescence microscopy. To measure apoptosis in the PE fat pad cells, we initially evaluated chromatin condensation (Fig. 6). The results indicate a lower uptake of the nuclear stain by the adipocytes of animals from group T, suggesting that they may possibly have a reduced rate of apoptosis relative to those of group S. Detraining did not appear to reverse this change.

DISCUSSION

The physical training program caused the desired aerobic adaptations because of the significantly increased maximal CS activity. These aerobic adaptations were completely reversed by detraining. It was shown that physical training increases mitochondrial biogenesis in skeletal muscle, which was accompanied by an increase in CS activity (20). Recently, it was reported that exercise increased the number and activity of mitochondria in adipocytes, measured by increases in the activity of mitochondrial markers: cytochrome c oxidase subunit IV (COX IV), cytochrome c oxidoreductase subunit I (CORE 1), PPARγ coactivator 1 (PCG1-α), and mitochondrial transcription factor A (Tfam) (40).

During the first 8 wk of training (before detraining), the body weight gain rate was lower in the trained than in the sedentary animals. In the last 4 wk, the detrained animals accelerated their weight gain rate and completely recovered it, reaching the sedentary group (Table 2). Training reduced the adipocyte size while physical detraining caused adipocyte hypertrophy (Fig. 2). Additionally, physical detraining completely restored the PE fat pad weight (Table 2). As shown previously (41), physical detraining in rats subjected to a high-fat diet increased their ability to store fat in the urogenital, retroperitoneal, and mesenteric fat pads. Such increase in fat stores with physical detraining has been attributed to several factors, including increased insulin sensitivity and increased activity of lipoprotein lipase (3, 10).

Leptinemia was noticeably lower in the trained animals. The lower weight gain followed by a decrease in the overall adiposity is among many factors that contributed to the results. In a previous work with rats trained for 8 wk, we had shown a significant reduction of leptinemia compared with sedentary animals (7). We could therefore infer that the reduction in leptinemia occurred at the expense of reduced adiposity and not because of the physical exercise. It is reasonable to admit that as catecholamines increase the intracellular cAMP (cyclic adenosine monophosphate) concentrations via β-adrenergic receptors during exercise and inhibit both the biosynthesis and the release of leptin by adipocytes (28, 39).

Physical training definitely improved lipidemia, since it lowered serum total cholesterol and TAG in T animals compared with group S, and these parameters returned to baseline (similar to group S) after detraining (Table 3). Physical training, especially aerobic, contributes to maintain cholesterol and TAG serum levels in a lower range (19, 38).

The biosynthesis of TAG in adipose tissue is a process closely linked to glucose metabolism. Figure 3, A and B, reveals differences in the lipogenic capacity in PE isolated
adipocytes between detrained and trained animals. In Fig. 3E, 14C-acetate was used to assess the de novo lipogenesis (DNL) since the only way this tracer can get into TAG is by its incorporation into the FA moiety. This maneuver showed that the DNL process followed the same tendency, i.e., it was reduced in trained animals and completely recovered after 4 wk of training interruption. Reinforcing this impression, the elevated malic and FAS activities (Fig. 4, A and B) contributed to increase lipogenesis in detrained group. According to a previous study in which epididymal fat was assessed (37), physical training allowed the improvement of glucose uptake by increasing the amount and activity of GLUT4. However, this increase in glucose uptake did not alter the adipocyte lipogenic capacity in trained animals, suggesting that a consistent amount of glucose was directed to another metabolic route in the PE adipocytes, possibly its oxidation to CO2 and H2O or lactate generation.

Another reason for the reduced adipose mass is the hypotrophy of mature adipocytes, perhaps as a result of increased lipolysis of trained compared with sedentary individuals of the same species (4).

In our lipolytic assays, adipose cells from trained rats showed decreased lipolytic capacity when maximally stimulated, with no differences in basal rates of lipolysis (Fig. 3, G and F, respectively). It is known that adipocyte triglyceride lipase (ATGL) is upregulated by regular exercise. In addition, exercise-induced reductions in circulating insulin also correlate with the typically higher levels of ATGL in primary adipocytes (29). However, the reduction in the maximal lipolytic capacity observed in our study may possibly be explained by the smaller size of adipocytes and by the fact that insulinemia was not decreased in trained animals. During bed rest, healthy young adults showed more intense glucose uptake and a weaker lipolytic activity compared with nondiabetic first-degree relatives (FDRs) of type 2 diabetic patients (15). These results support the hypothesis that cessation of exercise in otherwise normal individuals evokes certain metabolic adaptations that lead to an increment in fat pad mass, not only by enhancing lipogenic activity but also probably by slowing down the lipolytic activity.

As shown in Fig. 5A, we can observe that both physical training and detraining significantly influenced the expression of the PPAR-gamma transcription factor. Adipogenesis is modulated by a cascade of transcription factors, including PPARγ and the C/EBP family. Figure 5B represents the quantification of PREF-1 cDNA, an important marker of the presence of preadipocytes and, also, is a known inhibitor of adipocyte differentiation (35). The exercise training seemed to upstimulate the increased expression of this gene and detraining somehow downregulated it. Higher expression of PREF-1 inhibits the differentiation of 3T3-L1 preadipocytes into adipocytes. Interestingly, physical detraining decreased the PREF-1 mRNA expression, bringing it back to the level seen in the sedentary group, which may favor the triggering of an adipogenic process.

Even the increased PPARγ gene expression, considered the master gene of adipogenesis, in group T (Fig. 5C) was not sufficient to promote cell differentiation because the amount of adiponectin, used here as a marker of differentiated adipocytes, in the vascular stroma of the T animals was not higher than that seen in sedentary animals. Recent observations indicated that the mRNA expression of glycerol-3-phosphate dehydrogenase (GPDH), a marker of adipocyte differentiation in the vascular stroma of trained rats, was significantly lower than in control rats. Furthermore, the mRNA expression of regulators of G-2 protein signaling (RGS2), which is induced during the early stage of adipocyte differentiation of 3T3-L1 cells and promotes adipocyte differentiation, was also downregulated in the vas-
cular stroma of trained rats, strongly suggesting that physical training can suppress the adipogenesis process (18, 24).

In support of this hypothesis, it was detected in detrained animals a significant increase in adiponectin gene expression in the vascular stroma, suggesting an increased amount of newly differentiated adipocytes (Fig. 5C). It is reported here that physical detraining significantly reduced the PREF-1 expression to levels equivalent to the S group (Fig 5B), suggesting a fall in the preadipocyte number and the withdrawal of an adipogenic suppressing factor. Moreover, the sustained increase in PPARγ gene expression in the detrained group reinforces the hypothesis that detraining creates an environment favorable to the process of adipogenesis (Fig. 5A).

We observed that physical training resulted in a significant reduction in the proportion of nuclei with condensed chromatin and that detraining was ineffective to reverse this process (Fig. 6). As aerobic exercise mobilizes fatty acids more intensely, it may preserve adipose cells viability. A previous study demonstrated a significant reduction in cardiac tissue apoptosis in the trained animals, showing a protective effect of exercise on cardiomyocytes (36). Moreover, exhaustive exercise caused damage to cellular DNA, rising the rate of apoptosis, in consequence of the increasing inflammatory processes and immunological changes that follows (27). In our study, the PE fat pad showed a higher fat cell number, maybe due to a reduced rate of cell loss throughout the entire process.

In conclusion, our results showed that 4 wk of physical detraining in rats allowed, among other effects, total adiposity recovery by increasing the lipogenic capacity relative to group T. We also observed that physical detraining may have stimulated the adipogenic process and attenuated apoptotic events which may contribute to rapidly recover the adipose mass.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).