Increased subsarcolemmal lipids in type 2 diabetes: effect of training on localization of lipids, mitochondria, and glycogen in sedentary human skeletal muscle

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Endurance-trained athletes exhibited less subsarcolemmal lipid volume than nonendurance-trained controls, with a significant inverse association between insulin sensitivity and SS lipid volume. Obese controls had threefold higher volume of subsarcolemmal lipids than type 2 diabetic patients. Thus many have suggested that high IMCL levels per se do not influence insulin sensitivity but represent a marker of increased fatty acid metabolites such as diacylglycerol (DAG), ceramide, and long-chain acyl-CoAs, which in turn could be detrimental for insulin sensitivity.

Several physiological processes have been shown to be compartmentalized in skeletal muscle. With differential centrifugation, IMF and SS mitochondria have been fractionated, and distinct biochemical and physiological properties have been shown. Advances in confocal imaging techniques have revealed compartmentalized GLUT4 translocation, where GLUT4 vesicle movement of longer distances only took place in the SS region, and a high-fat-fed diet reduced GLUT4 translocation in the t-system to a greater extent than in the sarcolemma.

Improvement of insulin sensitivity in type 2 diabetic patients can be achieved by regular physical activity. Therefore, endurance training of type 2 diabetic subjects is an experimental model capable of unraveling factors implicated in impaired insulin sensitivity. Thus, to discover whether compartmentalization of energy stores and mitochondrial energy metabolism has proven to be important for normal muscle function.

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index (BMI)-matched control subjects pre- and post-10 wk of aerobic training. We hypothesized that 10 wk of aerobic training would increase the content of mitochondria and glycogen and decrease the content of lipids in the SS region to a greater extent than in the IMF region.

**MATERIALS AND METHODS**

**Subjects.** Twelve male type 2 diabetic subjects and 12 male age- and BMI-matched subjects were included in the study (Table 1). Other aspects of the study have recently been published (27). The control subjects had no family history of type 2 diabetes, and none was taking medication. In the diabetic group, six were taking metformin, one was taking sulfonylurea, and four were taking both drugs. None was taking with insulin. Seven were treated with antihypertensives and six with lipid-lowering agents. All medications were withdrawn 7 days before the pre- and posttraining clamp studies (see below) including muscle biopsies. Patients were all glutamic acid decarboxylase 65 antibody negative and without signs of diabetic retinopathy, neuropathy, nephropathy, or macrovascular complications. All subjects had normal results on blood test screening for hepatic and renal function and had no cardiovascular disease. All subjects gave written informed consent, and the study was approved by the local Ethics Committee of Funen and Vejle County and was performed in accordance with the Helsinki Declaration. For relevant comparison, unpublished data from control biopsies from elite Norwegian cross country skiers (n = 10; maximal oxygen uptake (Vo2max) = 86.5 ± 1.5 ml·min⁻¹·kg⁻¹; age: 22 ± 0.5 yr; weight: 80.2 ± 2.8 kg; BMI: 24.3 ± 0.5) and high-level soccer players (n = 5; Vo2max = 53.1 ± 2.0 ml·min⁻¹·kg⁻¹; age: 27 ± 1.5 yr; weight: 79.0 ± 3.1 kg; BMI: 24.5 ± 0.6) were included in the study.

**Training program.** The subjects participated in an aerobic training program for 10 wk. The training consisted of cycling on stationary bikes including sessions of both continuous and interval exercise of 20–30 min of duration four to five times per week. Training intensity was in the first 6 wk 63 ± 2% and in the last 4 wk 70 ± 2% of pretraining Vo2max. Details of the training program and compliance have been reported previously (27).

**Test protocols.** Before and after training, subjects performed a graded maximal exercise test to determine Vo2max and underwent a euglycemic-hyperinsulinemic clamp test (3-h insulin infusion, 80 mU·min⁻¹·m⁻²) to assess insulin-stimulated glucose disappearance rate (Rd) as described previously (27). The tests were conducted on separate days, and the subjects were instructed to abstain from physical training and strenuous physical activity 48 h before the tests. Plasma glucose, glycated hemoglobin (HbA1c), serum insulin, free fatty acid, cholesterol, triglycerides, low density lipoprotein, and high density lipoprotein were measured as described previously (12). Muscle biopsies were obtained from the vastus lateralis muscle on the day of the clamp test before insulin infusion using a modified Bergström needle with suction under local anesthesia (10 ml lidocaine 2% injected sc).

**Transmission electron microscopy.** Muscle specimens were fixed with 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.3) for 24 h and afterwards rinsed four times in 0.1 M sodium cacodylate buffer. Following rinsing, muscle specimens were postfixified with 1% osmium tetroxide and 1.5% potassium ferrocyanide in 0.1 M sodium cacodylate buffer for 90 min at 4°C. The use of reduced osmium tetroxide containing potassium ferrocyanide is favoring a high electron density of glycogen particles (7). After postfixation, the muscle specimens were rinsed twice in 0.1 M sodium cacodylate buffer at 4°C, dehydrated through a graded series of alcohol at 4–20°C, infiltrated with graded mixtures of propylene oxide and Epon at 20°C, and embedded in 100% Epon at 30°C. To obtain as many fibers as possible, the ultra-thin sections were cut (using a Leica Ultracut UCT ultramicrotome) in three steps separated by 150 nm. The sections were contrasted with uranyl acetate and lead citrate and examined and photographed in a precalibrated Philips EM 208 electron microscope and a Megaview III FW camera. In the sections from the three depths of each biopsy, all of the longitudinally oriented fibers were included obtaining a mean of nine fibers per biopsy (range: 6–11). From each fiber, 24 images were obtained at ×40,000 magnification in a randomized systematic order, including 12 from the SS region and 6 from both the superficial and central region of the myofibrillar space (Fig. 1). The variation in the parameters between images was used to estimate a coefficient of error (CEest) as proposed for stereological ratio-estimates by Howard and Reed (15).

**Lipid, mitochondria, and glycogen volume and localization.** The following two pools of IMCL were defined: IMF lipids and SS lipids (Fig. 2). Point counting (9) was used to estimate the IMF lipid volume density of the myofibrillar space and the SS lipids as a volume per surface area of fiber. Thus the estimate of SS lipids is unbiased of training-induced changes in other parameters as mitochondria and glycogen volume. The CEest was 0.48 and 0.37 for IMF and SS lipid volume fractions, respectively. The volume of mitochondria was estimated by point counting. The following three localizations were defined: central IMF, superficial IMF, and SS (Fig. 1). The IMF mitochondria were expressed relative to the myofibrillar space and the

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**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Pretraining</th>
<th>Posttraining</th>
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<tbody>
<tr>
<td></td>
<td>Type 2 diabetes</td>
<td>Control</td>
</tr>
<tr>
<td>Age, yr</td>
<td>53 ± 1</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>108.2 ± 2.2</td>
<td>110.3 ± 3.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.5 ± 1.0</td>
<td>33.2 ± 0.7</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>31.8 ± 1.8</td>
<td>32.0 ± 1.4</td>
</tr>
<tr>
<td>Vo2max, ml·min⁻¹·kg⁻¹</td>
<td>21 ± 1</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>6.7 ± 0.3e</td>
<td>5.8 ± 0.1</td>
</tr>
<tr>
<td>Fasting serum insulin, pmol/l</td>
<td>62 ± 7</td>
<td>78 ± 13e</td>
</tr>
<tr>
<td>Fasting serum FFA, μmol/l</td>
<td>503 ± 47</td>
<td>383 ± 34</td>
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<tr>
<td>Triglycerides, mmol/l</td>
<td>5.0 ± 0.2</td>
<td>4.8 ± 0.2</td>
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<tr>
<td>Cholesterol, mmol/l</td>
<td>5.0 ± 0.2</td>
<td>4.8 ± 0.2</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>2.8 ± 0.2e</td>
<td>2.8 ± 0.2e</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.3 ± 0.3e</td>
<td>5.2 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 12 subjects. BMI, body mass index; Vo2max, maximal oxygen uptake; FFA, free fatty acid; HDL, high density lipoprotein; LDL, low density lipoprotein; HbA1c, glycated hemoglobin; Rd, insulin-stimulated rate of glucose disappearance. Interaction of training and group (P < 0.01); different from pretraining (P < 0.05); main effect of training (P < 0.05); n = 10; main effect of group (P < 0.05); n = 11.

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IMF and intramyofibrillar fractions to volume per fiber surface area. Assuming fibers of cylindrical shape, the volume beneath the surface area of fiber (V_f) is: $V_f = \pi \cdot 0.5 \cdot A$, where $R$ is fiber radius and $A$ is the fiber surface area. When fiber radius is assumed to be 40 μm and fiber surface area is 1 μm², the volume beneath the surface area of fiber is 20 μm³. Thus the volume fractions of IMF and intramyofibrillar parameters are multiplied with a factor of 20 when relative comparison with SS parameters is conducted and total values are calculated.

**Statistics.** Statistical analyses were performed using **STATA 10.1 (Stata Statistical Software: Release 10; StataCorp, College Station, TX).** All interactions or main effects were tested using a linear mixed-effects model with subjects as random effect and with training, group, and location as fixed effects. Variables with skewed distributions were log-transformed before analysis. When data did not reach normal distribution and equal variance, the nonparametric Kruskal-Wallis test was used. Relationships between continuous variables were investigated using Pearson's correlation analysis. Significance level was accepted at $P < 0.05$.

**RESULTS**

A comprehensive description of the subjects is presented in Table 1 and can also be found in a companion paper (27). Briefly, type 2 diabetic patients had higher HbA1c, fasting glucose, and plasma triglyceride levels and lower insulin sensitivity compared with control subjects (Table 1). Training induced an ~20% increase in insulin sensitivity in both groups and a slight but significant decrease in HbA1c in type 2 diabetic patients (Table 1).

**IMCL localization.** Median [interquartile range (IQR)] total volume percentages of IMCL in type 2 diabetic patients was 20% increase in insulin sensitivity in both groups and a slight but significant decrease in HbA1c in type 2 diabetic patients.
0.66 (0.36 – 1.43) pretraining and 0.65 (0.37 – 1.24) posttraining. Lower values were observed in control subjects: 0.33 (0.28 – 0.58) pretraining and 0.35 (0.28 – 0.87) posttraining (main effect, \( P < 0.03 \)). Training did not change the total volume percentage of IMCL (\( P = 0.80 \)), and no interaction with group of subjects was found (\( P = 0.24 \)). Corresponding values were in elite cross country skiers (0.52 (0.37 – 0.85)) and in soccer players (0.42 (0.24 – 0.82)), which were not different from type 2 diabetic patients and control subjects (\( P = 0.25 \)).

Two subcellular fractions of IMCL were defined based on their localization in either the SS or IMF space. This revealed that type 2 diabetic patients had a 3.1-fold higher level of SS lipids in the pretraining condition compared with control subjects (\( r^2 = 0.29, P = 0.07 \)) and control subjects (\( r^2 = 0.26, P = 0.09 \)). Regarding pretraining total lipid volume, an inverse relationship with insulin sensitivity was found in type 2 diabetic patients (\( r^2 = 0.27, P = 0.08 \)). No relationships between fractions of lipids and insulin sensitivity were observed posttraining or when using delta values (post-pre values).

**Mitochondria.** Control subjects and type 2 diabetic patients had an equal volume fraction of total mitochondria pretraining, as measured as \( R_d \) (\( r^2 = 0.62, P = 0.002 \); Fig. 4). No such relationship was observed in control subjects (\( r^2 = 0.05, P = 0.51 \)). The pretraining level of IMF lipids tended to be inversely related to insulin sensitivity in both type 2 diabetic patients (\( r^2 = 0.29, P = 0.07 \)) and control subjects (\( r^2 = 0.26, P = 0.09 \)).

**Correlation analysis showed a strong inverse relationship between pretraining levels of SS lipids and insulin sensitivity measured as \( Rd \) (\( r^2 = 0.62, P = 0.002 \); Fig. 4). No such relationship was observed in control subjects (\( r^2 = 0.05, P = 0.51 \)).**
and the training mediated an increase (~40%) of similar magnitude in both groups (Table 2). TEM revealed distinct compartments and regions of mitochondria in muscle fibers. Concerning mitochondria volume, there was no difference between type 2 diabetic patients and control subjects in either of these localizations (Table 2). In relative terms (median and IQR), 10.6% (9.1–12.6) of the total mitochondria were localized in the SS region, 68.9% (65.3–73.8) in the superficial IMF region, and 17.5% (14.2–22.9) in the central IMF region. The training-mediated increase was dependent on localization (P = 0.001) and not different between groups (P = 0.36). Post hoc analysis revealed that the relative increase in median SS mitochondria (124%) was greater than in both superficial IMF (64%) and central IMF (14%) mitochondria (P = 0.02 and P < 0.001, respectively). The increments in central and superficial IMF mitochondria were not different (P = 0.10). No associations between mitochondria volume and insulin sensitivity could be detected.

**Glycogen.** As with mitochondria, the type 2 diabetic patients had volume fraction of total glycogen pretraining equal to control subjects, and the training mediated an increase (25%) of similar magnitude in both groups (Table 2). The glycogen volume was estimated in three distinct localizations. The relative distribution was not different between groups, pretraining values (median and IQR) were 84.4% (81.5–87.2) as IMF, 15.6% (13.8–17.8) as intramyofibrillar glycogen (IMF), and 10% (8%–12%) as SS glycogen. The increase in glycogen following training was not different between groups (P = 0.78); however, there was a localization effect (P < 0.0001). Post hoc analysis showed that the median relative increase in SS glycogen (91%) was greater compared with the increase in IMF (49%) and intramyofibrillar glycogen (16%) (P = 0.0004 and P = 0.002, respectively), whereas no difference was found between the relative increments in IMF and intramyofibrillar glycogen (P = 0.50).

The average ± SE particle volume of glycogen increased (23%) from 13,619 ± 431 nm³ (diameter of 29.5 ± 0.3 nm) pretraining to 16,660 ± 470 nm³ (diameter of 31.6 ± 0.3 nm) posttraining. Glycogen volume in none of the three localizations was associated with insulin sensitivity. Discrimination between type I and II fibers based on the mitochondrial volume density and Z-line width revealed that no fiber type differences were present in any of the three localizations of glycogen (data not shown). This was observed in type 2 diabetic patients and control subjects both before and after training.

**DISCUSSION**

Patients with type 2 diabetes have altered fat metabolism with elevated lipid metabolites in blood and tissues, which has been linked to decreased insulin sensitivity. The high magnification of TEM allows visualization of intramuscular lipid droplets, revealing that lipid droplets are localized in the fibers both just beneath the sarcolemma, a SS fraction, and in between the myofibrils throughout the interior of the fiber, an IMF fraction. This study is, to our knowledge, the first using electron microscopy to address the role of these two distinct fractions of IMCL in type 2 diabetes and training. Three novel aspects were discovered: 1) an abnormal lipid distribution with threefold higher volume of lipids in the SS region and similar volume density of IMF lipids in sedentary type 2 diabetic patients compared with BMI-matched control subjects and highly endurance trained subjects; 2) a strong inverse relationship between pretraining levels of SS lipid and insulin sensitivity in type 2 diabetic subjects; and 3) an aerobic training-mediated decrease in SS lipids of type 2 diabetic patients approaching the levels of control subjects. Together, this demonstrates an abnormality of SS lipids in type 2 diabetes, which could be an important factor contributing to the regulation of skeletal muscle insulin sensitivity.

The present data confirm previous reports (8, 23) showing that type 2 diabetic subjects have higher total IMCL content compared with BMI-matched control subjects. Endurance training has previously been shown to lower the content of IMCL in type 2 diabetic patients (4, 19). However, in nondiabetic untrained subjects, endurance training often elevates the IMCL content (10, 14, 18, 33). These increments in total IMCL seems to be achieved after training periods at medium intensity (60% of maximal oxygen uptake) with sessions exceeding 1 h in duration (18, 33). One study with sessions of higher intensity (72%) and shorter duration (30 min) found only an increase in type II fibers (14). Furthermore, a study with varying intensity...
(65–85%) and ~1-h sessions found only an increase in total IMCL if the training period included a high-fat diet (10). Thus it is likely that a combination of the higher training intensity (62–70%), shorter session duration (30 min), and normal diet composition explains why total IMCL was not increased following the training period in the present study. However, importantly, our results suggest that aerobic training has different effects on two distinct fractions of IMCL. We found that sedentary type 2 diabetic patients had a threefold higher pre-training level of SS lipids compared with control subjects, and, although training halved this pool of SS lipids, the IMF lipids were unchanged. In control subjects, both SS and IMF lipids were unchanged following training.

Recently, van Loon et al. (41) used fluorescence microscope and Oil red O staining, a procedure with the lower resolution of light microscopy, to compare IMCL localization in type 2 diabetic patients with highly endurance-trained athletes and lean sedentary. In successive bands of 2 μm in width from the sarcolemma toward the central of each fiber, they found no difference in the relative distribution pattern of lipids between groups. This is in agreement with a previous study using the same method on obese subjects before and after endurance training and diet intervention (24). In spite of different methods used, it is in contrast to our results showing an accumulation of SS lipids in type 2 diabetic patients compared with both BMI-matched controls and highly endurance-trained athletes. This is likely explained by the insensitivity of the 2-μm band method, used in the two studies, to precisely define and thus estimate the lipid volume in the SS region. The width of the SS region depends on the presence of lipids, nuclei, mitochondria, glycogen, and capillaries in connection to the fiber. Thus, in a fiber, the width of the SS region can vary from almost zero up to 10 μm in the extreme. A 2-μm band could therefore contain IMF lipids and, likewise, SS lipids could reach deeper than 2 μm, confounding the true measure of a SS lipid fraction.

IMCL has been implicated in type 2 diabetes based on correlation analysis, showing strong negative associations between total IMCL content and insulin sensitivity in sedentary subjects (20, 30, 32). However, this association disappears with the inclusion of endurance-trained subjects, because they have elevated IMCL levels and, at the same time, are highly insulin sensitive (8, 16, 41). The contradictions have been termed the “athlete paradox.” Our results suggesting that the distribution of IMCL in SS and IMF fractions is different between the above-mentioned group of subjects provide one explanation for this contradiction.

Fatty acid metabolites such as DAG and ceramide concentrations were recently measured in both a membrane-bound and a cytosolic fraction when overexpressing carnitine palmitoyltransferase-1 in rats (3). This revealed a selective decrease in the membrane-bound DAG, which was associated with an inhibition of protein kinase (PKCζ), ultimately leading to improved insulin sensitivity. With the reservation that lipid localization in rodents could be different from that in humans, this membrane-bound fraction of DAG could represent a sarcolemmal pool, supporting our results suggesting a role of lipids in modulating insulin sensitivity in the SS region. The higher SS lipid content found in the type 2 diabetic patients can be explained by elevated lipid availability and/or diminished SS mitochondria lipid oxidative capacity. The blood profile with elevated plasma triglycerides indicates elevated lipid availability in the type 2 diabetic patients. There was no difference in SS mitochondria volume between groups (Table 2); however, this does not necessarily reflect the lipid oxidation capacity. Lipid oxidation is a complex process involving several steps, including β-oxidation, tricarboxylic acid cycles, and electron transport chain. Ritov et al. (35) showed that the electron transport chain activity was suppressed, particularly in SS mitochondria in type 2 diabetic patients, compared with BMI- and age-matched subjects. A study using rats showed a lower lipid oxidation rate in SS mitochondria compared with IMF mitochondria, and that a modest overexpression of PGC-1α selectively increased the lipid oxidation rate in SS mitochondria and concomitantly increased insulin sensitivity (2). If type 2 diabetic patients have impaired SS mitochondrial lipid oxidation capacity, it can explain the observed accumulation of SS lipids in these patients.

The question emerges as to what is the difference between IMF and SS lipids? The structure of the muscle cell with a highly developed transverse tubular system (t-system) connecting the interior of the cell with the surface should be recognized. The IMF lipids are often found very close to the mitochondria in remote positions from the t-system, which is almost exclusively surrounded by the sarcoplasmatic reticulum. In the SS region, lipids often touch the sarcolemma (Fig. 5), and in this region the t-system is not surrounded, and may be protected, by the sarcoplasmatic reticulum. Thus SS lipids might more easily interfere with key proteins involved in the insulin signaling cascade than IMF lipids. More detailed insights in the difference between SS and IMF lipids could be

Fig. 5. TEM images of the subsarcolemmal region. TEM images illustrating the difference in subsarcolemmal lipid accumulation pretraining between type 2 diabetic patients (A) and control subjects (B) (original magnification ×13,000, scale bar = 2 μm). The white circular areas are lipid droplets.
obtained by intervention studies with inclusion of anti-diabetic drugs and diet alterations.

Although the decrease in SS lipids was accompanied by improved insulin sensitivity in type diabetic patients, insulin sensitivity was still significantly reduced after training while the difference in SS lipids was abolished compared with obese control subjects. Moreover, the inverse association between pretraining levels of SS lipid and insulin sensitivity observed in type 2 diabetes disappeared following the 10 wk of aerobic training. This is in accordance with a previous report using biochemically determined intramuscular triacylglycerol (4). This can be interpreted as 1) mainly in sedentary subjects, high SS lipids contribute to impaired insulin sensitivity and 2) excess amount of SS lipids are not the single cause of impaired insulin sensitivity; hence, other factors related to impaired insulin sensitivity (e.g., cytokines and hormones) were not improved.

In the present study, as in the previous work (4), plasma glucose and triglycerides remained elevated posttraining in the type 2 diabetic patients and, furthermore, the patients did not reduce their body mass.

Studies comparing weight-matched, nondiabetic subjects have shown both lower (5, 23, 37) and equal (39) content of muscle glycogen in type 2 diabetes. However, recently, we have demonstrated that distinct subcellular fractions of glycogen have different roles in muscle function (29). Thus we aimed to investigate the role not only of glycogen content but also glycogen localization in type 2 diabetes and training. Although there were no type 2 diabetes-related differences, the increase in glycogen content following endurance training was highly localization dependent. The SS glycogen was more than doubled, whereas IMF and intramyofibrillar glycogen only increased by ~20%. The volume of glycogen particles increased by 23%, which indicates that the increase in IMF and intramyofibrillar glycogen was accounted for by adding glucose residues to existing particles, in contrast to the increase in SS glycogen where an increase in the number of particles might have occurred as well. This is a novel indication of compartment-dependent biosynthesis of new glycogen particles. Together with lipid and mitochondria, glycogen adaptations to aerobic training predominantly occur in the SS region, indicating, in general, a role of proximity to the sarcolemma, interstitium, and capillary, or a mechanical component related to proteins exclusively situated in the sarcolemma in aerobic training adaptations.

In conclusion, this study, estimating intramyocellular localization of lipids, mitochondria, and glycogen using TEM, indicates that type 2 diabetic patients are exposed to an increased content of lipids localized just beneath the sarcolemma. This was found both with non-diabetic matched control subjects and endurance-trained athletes. Interestingly, aerobic training was found to lower this excess SS lipid content by ~50%, approaching the levels observed in the non-diabetic subjects. Thus consideration of cell compartmentation may advance the understanding of the role of lipids in muscle function and type 2 diabetes. The distribution and content of glycogen and mitochondria in different compartments was not different in type 2 diabetic patients compared with matched control subjects; however, the increase in glycogen content following training indicated a subsarcolemmal location for new glycogen particle biosynthesis.

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DISCLOSURES

No conflicts of interest are declared by the authors.

REFERENCES


