Muscle Characteristics and Substrate Energetics in Lifelong Endurance Athletes

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ABSTRACT


Purpose: The goal of this study was to explore the effect of lifelong aerobic exercise (i.e., chronic training) on skeletal muscle substrate stores (intramyocellular triglyceride [IMTG] and glycogen), skeletal muscle phenotypes, and oxidative capacity (ox), in older endurance-trained master athletes (OA) compared with noncompetitive recreational younger (YA) athletes matched by frequency and mode of training.

Methods: Thirteen OA (64.8 ± 4.9 yr) exercising 5 times per week or more were compared with 14 YA (27.8 ± 4.9 yr) males and females.

IMTG, glycogen, fiber types, succinate dehydrogenase, and capillarization were measured by immunohistochemistry in vastus lateralis biopsies. Fat-ox and carbohydrate (CHO)-ox were measured by indirect calorimetry before and after an insulin clamp and during a cycle ergometer graded maximal test. Results: VO₂peak was lower in OA than YA. The OA had greater IMTG in all fiber types and lower glycogen stores than YA. This was reflected in greater proportion of type I and less type II fibers in OA. Type I fibers were similar in size, whereas type II fibers were smaller in OA compared with YA. Both groups had similar succinate dehydrogenase content. Numbers of capillaries per fiber were reduced in OA but with a higher number of capillaries per area. Metabolic flexibility and insulin sensitivity were similar in both groups. Exercise metabolic efficiency was higher in OA. At moderate exercise intensities, carbohydrate-ox was lower in OA but with similar Fat-ox.

Conclusions: Lifelong exercise is associated with higher IMTG content in all muscle fibers and higher metabolic efficiency during exercise that are not explained by differences in muscle fibers types and other muscle characteristics when comparing older with younger athletes matched by exercise mode and frequency. Key Words: AGING, CHRONIC EXERCISE, MUSCLE FIBERS, CAPILLARY DENSITY, ENERGY EXPENDITURE, SUBSTRATE OXIDATION, INSULIN SENSITIVITY

Aging is associated with a decline in physical capacity and modifications of muscle phenotype (34), leading to increased overall morbidity and risk for development of cardiometabolic diseases. Aerobic training interventions suggest that aged skeletal muscle remains malleable to sustain the functional and metabolic demands of exercise (7) demonstrated by a shift toward higher content of type I fibers and relative decrease in type IIx fibers (29), increased fiber cross-sectional area (22), enhanced oxidative capacity (39), capillary angiogenesis (35), and elevated glycogen stores (33). Further, we have previously demonstrated that chronic aerobic training in older adults increases intramyocellular triglyceride (IMTG) stores (9) and reliance on fat metabolism (1) during exercise.

Despite the growing body of literature demonstrating alterations in skeletal muscle substrate content and capacity for oxidation in previously sedentary subjects, few studies have compared chronic aerobic training adaptations in young and old athletes. Current evidence supports the notion that being physically active throughout a person’s life (life-long) protects oxidative fiber number and size, as well as mitochondrial function when compared with younger trained (39) and older sedentary (2,45) subjects. These retained muscle adaptations to exercise seem to provide functional benefits, such as improved balance, gait speed, and ability to get up from a chair (45), which in turn are likely to improve...
quality of life and reduce the risk of falling. Yet, the impact of lifelong aerobic training on skeletal muscle metabolism within the context of whole-body substrate oxidation and insulin sensitivity is still largely unknown.

The primary goal of this study was to determine skeletal muscle substrate storage and capacity for oxidation, as well as exercise metabolic efficiency in older master athletes and younger subjects matched by frequency and mode of training. A secondary goal was to determine if differences in skeletal muscle substrate storage were associated with differences in substrate oxidation under different physiological conditions. We hypothesized that despite lower peak aerobic capacity in older master athletes, lifelong aerobic training in this group would result in similar skeletal muscle substrate storage compared with the younger athletes matched by exercise mode and frequency, as well as similar oxidative capacity, metabolic efficiency, and substrate oxidation under same physiological conditions.

**METHODS**

**Subjects.** Fourteen younger (age, 18–39 yr) and 13 older (age, 60–75 yr) endurance-trained athletes were recruited for this cross-sectional comparison. To be included, older women and men were training 5 or more structured aerobic exercise sessions per week either in running, cycling, swimming, or aerobic dancing (fitness classes). Younger athletes were non-competitive recreational athletes matched by frequency and mode of training with at least 3 yr of uninterrupted (>3 months) training. Habitual physical activity was self-reported and discussed during the screening visit medical interview, including exercise mode, frequency, and training years. All subjects were in general good health, nonsmokers, weight stable, and training stable for the last 6 months. The University of Pittsburgh Institutional review board approved the protocol, and all volunteers gave written consent.

**Body composition.** Total body fat-free mass (FFM), fat mass, and percent body fat were measured by dual-emission X-ray absorptiometry (Lunar Prodigy; GE Healthcare, Milwaukee, MI).

**Physical fitness.** VO\textsubscript{peak} was assessed by a graded exercise test on an electronically braked cycle ergometer (Excalibur; Lode B.V., Groningen, The Netherlands) in conjunction with indirect calorimetry (Moxus; AEI Technologies, Pittsburgh, PA). The initial workload was set depending on the sex and age of the individual (50 W for younger and older women, 75 W for older men, 100 W for younger men) for the first 2 min and then increased by 50 W (men) or 25 W (women) every 2 min thereafter until volitional exhaustion or one of the established criteria for VO\textsubscript{peak} had been reached (38). Heart rate, blood pressure, and ECG were recorded before, during, and immediately after this test.

**Skeletal muscle biopsies.** Percutaneous muscle biopsies were obtained from the vastus lateralis as described previously (2). Subjects were asked to refrain from exercise in the last 48 h before the biopsy. Subjects were admitted to the Clinical and Translational Research Center in the evening and received a standard dinner (7.5 kcal·kg\textsuperscript{-1}·body weight, 50% carbohydrate (CHO), 30% fat, and 20% protein). The biopsy was performed the following morning at 7 a.m. after an overnight fast. Samples were trimmed of all visible adipose tissue with a dissecting microscope (Leica EZ4; Leica Microsystems, Wetzlar, Germany) and blotted dry. The muscle specimen was mounted on a small piece of cork with mounting medium, placed in liquid nitrogen cooled isopentane, and then placed into liquid nitrogen. All samples were stored at −80°C until analysis.

**Immunohistochemistry.** Histochemical analyses were performed on 10-μm serial sections using methods previously described (9). IMTG content was determined by Oil Red O and fiber type co-stain (2), allowing fiber specific IMTG measurements and cross-sectional area. Succinate dehydrogenase (SDH) (complex II of the electron transport chain) staining was used as a marker of oxidative capacity (40). Glycogen content was measured using a standard Shiffs reagent protocol (23). Capillary density was determined as previously described (9). Capillary density was computed as the total number of capillaries per cross-sectional area of tissue (capillaries/area). The number of fibers in the cross-sectional area of tissue is reported as the ratio of fiber/area and the number of capillaries per fiber as the ratio of capillaries/fiber.

**Whole-body substrate oxidation and exercise efficiency.** Indirect calorimetry was used to measure VO\textsubscript{2} and VCO\textsubscript{2} under three physiological conditions: 1) in the fasted state between 6 and 7 a.m. (before the biopsy described above), 2) in the postprandial state at the end of an hyperinsulinemic euglycemic clamp, and 3) during the graded exercise test described above. Systemic rates of fat oxidation (Fat-ox) and CHO-ox were calculated using the adapted stoichiometric equations of Frayn (13):\[[\text{Fat-ox (mg·min}^{-1}]=1.67\text{VO}_2\text{(ml·min}^{-1})-1.67\text{VCO}_2\text{(ml·min}^{-1})\]  
\[[\text{CHO-ox (mg·min}^{-1}]=4.55\text{VCO}_2\text{(ml·min}^{-1})-3.21\text{VO}_2\text{(ml·min}^{-1})\]  

To compute the proportion of energy expended from CHO or fat, Fat-ox and CHO-ox were transformed in kilocalories per minute and expressed as a proportion of resting energy derived from fat or CHO as used previously (1). For substrate oxidation during the graded exercise test, only points corresponding to a respiratory exchange ratio less than 1 were used to account for possible changes in the size of the bicarbonate pool during maximal exercise (26). Protein oxidation rates were not included based on our laboratory’s prior work, demonstrating that rates of urinary nitrogen excretion were similar in different body phenotypes during resting conditions (18) and on the assumption that the amount of protein oxidized, as well as other metabolic processes, such as gluconeogenesis from protein, ketone body formation, and lipogenesis during exercise, are quantitatively negligible compared with glucose and fatty acid oxidation (37).
Table 1. Subjects’ characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Younger (7 M/7 F)</th>
<th>Older (9 M/4 F)</th>
<th>P Value (Two-Tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>27.8 ± 4.9</td>
<td>64.8 ± 4.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body weight (BW, kg)</td>
<td>65.66 ± 10.78</td>
<td>23.76 ± 2.50</td>
<td>0.958</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>22.12 ± 1.74</td>
<td>23.76 ± 2.50</td>
<td>0.958</td>
</tr>
<tr>
<td>Fat-free mass (FFM, kg)</td>
<td>53.29 ± 10.66</td>
<td>23.76 ± 2.50</td>
<td>0.958</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>12.03 ± 4.17</td>
<td>14.15 ± 7.79</td>
<td>0.395</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>18.68 ± 6.47</td>
<td>20.63 ± 10.76</td>
<td>0.578</td>
</tr>
<tr>
<td>V̇O₂peak (L.min⁻¹)</td>
<td>3.816 ± 1.088</td>
<td>3.031 ± 0.763</td>
<td>0.041</td>
</tr>
<tr>
<td>V̇O₂peak (mL.min⁻¹.kg FFM⁻¹)</td>
<td>70.53 ± 9.08</td>
<td>55.82 ± 7.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak power output (W)</td>
<td>285.7 ± 20.3</td>
<td>201.9 ± 13.4</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Mean ± SD.

RESULTS

Subject Characteristics

Subject characteristics are presented in Table 1. Training years were between ~35 and 40 yr for the older master athletes and 5 and 13 yr for younger subjects. FFM, fat mass, and percent body fat were not different between age groups. Younger athletes had a higher V̇O₂peak than the older athletes with a magnitude of ~25% when expressed relative to FFM. Self-reported activities were on average six sessions per week, with running as the most common physical activity (62%), followed by biking (23%), brisk walking, and aerobic fitness classes (both 8%). In addition to their main exercise mode, cross-training and seasonal activities included skiing, golfing, and swimming.

Skeletal muscle lipid storage is greater in older compared to younger endurance-trained athletes

Chronic aerobic training increases skeletal muscle substrate storage in young and old previously sedentary subjects. Yet the effects of lifelong aerobic training on skeletal muscle adaptations are largely unknown. Older athletes had higher content of IMTG in each fiber type measured (Fig. 1A), as well as overall greater content of IMTG. Glycogen content (Fig. 1B) was higher in young athletes compared to old, whereas no differences in succinate dehydrogenase (Fig. 1C) were noted.

Oxidative fibers are higher in older compared to younger endurance-trained athletes

Older athletes had higher proportion of type I fibers and lower type IIa fibers than younger athletes (Fig. 2A). The proportion of type IIx fibers was not different between groups. Mean area of type I fibers was similar in both groups, whereas younger athletes had larger IIa and IIx fiber areas (Fig. 2B). These

FIGURE 1—Skeletal muscle fiber type proportion (A) and cross-sectional area (B) in younger and older athletes. *P < 0.05 **P < 0.001 two tailed independent t test. MHC, myosin heavy chain.
data suggest that lifelong physical activity may not prevent the proposed age-related decline in type II fiber area (31).

**Capillary density is lower in older compared with younger endurance-trained athletes.** As skeletal muscle capillary density is affected by aging and type 2 diabetes (21) and is associated with oxidative capacity (9), we next determined if capillary density was associated with the observed differences in oxidative fibers. Although the number of capillaries per fiber was higher in the younger athletes (Fig. 3A), capillary density relative to muscle area was higher in the older athletes (Fig. 3B). These data suggest that the decline in capillary density associated with sedentary aging (21) is attenuated with lifelong aerobic exercise.

**Metabolic flexibility and insulin sensitivity are similar in older compared with younger endurance-trained athletes.** Given the observed differences in skeletal muscle substrate composition and capacity for oxidation, we next examined whether or not these differences translated into changes in whole-body substrate oxidation and insulin sensitivity. Older athletes had higher resting energy expenditure in fasting condition, whereas younger athletes had higher energy expenditure in postprandial condition (Fig. 4A; significant interaction $P = 0.01$). The proportion of substrate use during both states was comparable in both groups (Fig. 4B). Metabolic flexibility, originally defined by the overall change in respiratory quotient from fasting to postprandial (28) was similar in both groups (Fig. 4C; insulin effect $P < 0.0001$). Insulin-stimulated glucose uptake was similar in younger and older athletes (Fig. 4D), with no differences in nonoxidative and oxidative disposals. Together these data suggest that lifelong endurance training protects older adults from declines in metabolic flexibility and insulin sensitivity. Moreover, relative fat- and CHO-ox rates for basal and insulin-stimulated substrates use under nonexercising conditions are maintained throughout the lifespan with aerobic exercise.

**Exercise metabolic efficiency is enhanced in older compared with younger endurance-trained athletes.** We previously demonstrated that exercise training resulted in improved skeletal muscle oxidative capacity.
(9) and exercise efficiency (1) in previously sedentary older adults. Based on the differences in peak aerobic capacity and substrate storage in older athletes, we next calculated exercise metabolic efficiency during a graded exercise test. Older athletes had higher exercise metabolic efficiency compared with younger athletes ($G$ of 9.03% $T$ 0.32% and 8.03% $T$ 0.26%; $P$ = 0.02). Regression curves for each group, including slope and intercept, are presented in Figure 5A ($P$ = 0.02 [older] and $P$ = 0.13 [younger]). Stage by stage delta efficiency is presented in Figure 5B (2 $\times$ 5 MANOVA not significant, point by point independent $t$ tests are presented in the figure).

**Moderate intensity exercise CHO-ox rates are lower in older compared with younger endurance-trained athletes.** At moderate relative intensities, younger athletes had greater rates of CHO-ox compared with older (Fig. 5C). Fat-ox was higher in the younger at very low intensities (Fig. 5C). It is important to note that the removal of time points with respiratory exchange ratio greater than 1, to avoid underestimation of fat-ox and overestimation of CHO-ox due to a potential difference in the bicarbonate buffering system and excess nonoxidative CO$_2$ exhaled, reduces greatly the number of subjects included in the higher intensities measurements. Nevertheless, these data suggest that the observed increase in IMTG and oxidative fibers may contribute to the enhanced exercise metabolic efficiency.

**DISCUSSION**

The overall goal of this study was to investigate chronic aerobic exercise training on skeletal muscle substrate adaptations, as well as systemic oxidation in young and older endurance-trained subjects. To achieve this goal, we examined skeletal muscle phenotypes, as well as whole-body substrate utilization using indirect calorimetry in 2 cohorts of subjects with similar endurance training regimens. We found that, despite lower peak aerobic capacity, lifelong master athletes have

**FIGURE 4—Energy expenditure (A), substrate use at rest in the fasted and post-prandial phase (B), metabolic flexibility (C), and insulin-stimulated glucose uptake (D).** *Significant interaction effect, **Significant effect of time in 2 $\times$ 2 mixed MANOVA. RQ, respiratory quotient; CHO, carbohydrate; FFM, fat free mass.
higher IMTG and proportion of oxidative fibers compared to younger athletes. These differences were reflected in enhanced exercise metabolic efficiency with lower reliance on CHO-ox during exercise in the older subjects (at higher intensities). Together the data suggest that lifelong aerobic exercise not only attenuates the age associated decreases in muscle oxidative potential but also provides older endurance-trained subjects with an enhanced capacity for fatty acid oxidation.

Age-induced increases in intramyocellular lipids have been observed in previous human studies. Under sedentary conditions, this phenomenon is associated with a decline in muscle mass and strength (8,16), as well as decreased insulin action (36). Although decreases in muscle mass, fiber cross-sectional area, and shifts in fiber type composition may explain, in part, intramyocellular lipid deposition in sedentary conditions (8,19), this is not the case for the chronically trained older individuals in the current study. We have previously exposed that the “athlete’s paradox” observed in younger endurance-trained athletes (17) was also present in older endurance trained athletes compared with sedentary controls (2). A key novel finding in the present study is that older endurance-trained athletes have greater lipid, yet lower CHO stores, compared with younger athletes with similar training regimens. Although aging per se has been associated with increased lipid uptake (44), chronic exercise training increases factors associated with IMTG turnover (i.e., storage and lipolysis) (2). We hypothesize that the combination of these age- and exercise-related alterations in IMTG turnover likely mediates, in part, the increased IMTG in this cohort. Proteins involved in IMTG storage are elevated in exercise-trained muscle (2,4,10). Additional studies are needed to investigate whether these or other mechanisms for the increased IMTG storage are altered in older endurance athletes.

In contrast to higher IMTG levels, older subjects demonstrated lower muscle glycogen stores compared with younger subjects. Although controversial, there is a suggestion that glycolytic activity (6), as well as type II fiber proportion and size (discussed below), may be reduced with aging. However, aerobic exercise training in previously sedentary older adults has been demonstrated to increase muscle glycogen content (9). Possible explanations to the lower glycogen content in older trained subjects is that younger endurance athletes may engage in relatively more frequent high intensities and/or that younger athletes may have altered postexercise CHO consumption relative to older athletes, thus providing the necessary stimulus for

**FIGURE 5**—Delta efficiency and substrate use during graded exercise test in older and younger endurance trained athletes. Panel A represents the regression lines defining oxygen uptake as a function of power output. The insert is the magnification of the origin of the axis (box). *Significant difference on the slope but not on the intercept. Panel B is delta efficiency between consecutive stages. *P < 0.05, #P = 0.09 two-tailed independent t test. Panel C is carbohydrate and fat oxidation as a function of relative intensity of peak oxygen consumption. *P < 0.05 two-tailed independent t test.
enhanced glycogen storage (25). Nevertheless, lower glycogen content in our older athletes did not contribute to alterations in basal or insulin-stimulated rates of substrate oxidation. Rather, the functional relevance was only observed at maximal intensity exercise. These data support the notion that lifelong endurance training may better position older athletes for moderate intensity activities with relative higher fat oxidation, whereas young athletes may be positioned for high-intensity exercise (i.e., higher glycogen). Thus, the capacity for moderate high fat oxidation activity may be enhanced with lifelong endurance training.

Based on our novel demonstration of increased lipid stores with lifelong exercise training, we next examined the potential mechanisms associated with this phenomenon. Although several studies have suggested that aging results in the atrophy of type II fibers (20,39), with a relative increase of the area occupied by type I fibers (30), this is not without controversy. Our data suggest that lifelong exercise training is accompanied by a shift toward greater slow oxidative fibers with no change in the overall size of these fibers (45). Interestingly, not only was the relative percentage of glycolytic fibers decreased in older trained subjects, the mean area was also decreased. These data suggest that if an aging decrease in glycolytic fibers occurs, perhaps exercise training promotes a compensatory increase in oxidative fibers. This new harmony between type I and type II fibers observed in the aging and trained muscle may explain, at least in part, the distinction in substrate stores between older and younger muscle of endurance-trained athletes witnessed in this study.

Previous studies have demonstrated that, although master athletes have significantly higher peak fitness levels compared with sedentary age-matched controls (41), the age-related decline in fitness persists despite continuous training. Thus, as expected, V̇O₂peak, both absolute and adjusted to FFM, was higher in younger than older athletes. Peak fitness may be limited by two key peripheral factors, capillarization (3,24) and mitochondrial capacity (3). Although capillary density, relative to the number of fibers, was lower in older trained subjects, adjusting the data to the lower number and cross-sectional area of glycolytic fibers suggests that capillary density is not different between the cohorts (5). This interpretation is in accord with previous studies that found similar adaptations in capillarization between older and younger adults undergoing an exercise intervention (15,35).

With respect to mitochondria, it has been reported that mitochondrial respiration (21), mitochondrial biogenesis (32), and perhaps oxidative capacity and energy production decline with aging. However, it is generally accepted that aerobic exercise training, in both older (9) and younger (11) previously sedentary subjects, results in enhanced mitochondrial oxidative capacity. In agreement with data from Proctor et al. (39), we did not observe any differences in mitochondrial capacity between the cohorts in this study. Thus, the difference in V̇O₂peak observed in our younger and older athletes seems to be explained mostly by the central component. This is in agreement with previous studies suggesting that peripheral factors play an important role in the elderly in the response to endurance exercise training (33). Together our data suggest that although lifelong exercise training may not prevent the age-associated loss of skeletal muscle capillarization, the overall capacity for substrate oxidation, as well as overall fitness, is enhanced relative to sedentary subjects regardless of age (2).

Based on our demonstration of enhanced lipid stores and similar capacity for oxidation, we next examined whole-body substrate utilization under different physiological conditions. Previous studies have reported age-related declines in the capacity of skeletal muscle to oxidize fat in the fasting state and during exercise (42,44). In this study, higher energy expenditure at rest was not associated with differences in substrate selection in the older athletes. These data are in stark contrast to previous reports from sedentary subjects (27), demonstrating a significant reduction in resting energy expenditure in older subjects adjusted for FFM. We speculate that the increased basal energy expenditure may be due to the modest but not significant BMI and gender difference between the groups (see bellow). Nevertheless, our data clearly indicate that the lifelong training preserves basal energy expenditure, as well as rates of both fat and CHO-ox in the basal and insulin-stimulated conditions. Thus, lifelong exercise training preserves metabolic flexibility and substrate selection with aging.

During moderate intensity exercise, older athletes used fewer CHO for energy. These data are in agreement with our demonstration of greater muscle glycogen content in younger subjects. At maximal intensity, no conclusions can be drawn from our indirect calorimetry data due to the limitations of stoichiometric computations in anaerobic conditions. Intervention studies have concluded that previously sedentary older subjects undergoing endurance exercise interventions of 16 wk were able to improve their reliance of fat during a 1-h submaximal exercise (1,43), thus our data may be explained by the maintenance of substrate oxidation in older athletes as well as by the shift toward type I fibers. Interestingly in our cohort, the higher muscle efficiency observed in the older athletes during the graded exercise test cannot be explained by different substrate use during exercise, but may be influenced by the greater number of capillaries per fibers and the higher proportion of type I fibers (1). Together these data suggest that lifelong aerobic exercise preserves, or perhaps enhances, resting exercise expenditure, as well as metabolic flexibility and substrate oxidation under physiological conditions.

This study is not without limitations. First, training regimens (frequency, mode) were self-reported. However, our data are in accord with previous reports of overall fitness and body composition in older and younger athletes (5,39). Although we attempted to include equal numbers of males and females, males represent 50% in the younger group and 69% in the older group. While the chi-square test for
sampling distribution was not significant, this discrepancy may influence some of the results. We believe that if so, this would have been in disfavor of the older group as women have relative lower exercise capacity and higher insulin sensitivity than men and thus, if the gender balance was important, we would have probably seen unequal insulin sensitivity and markers of oxidative capacity between our two groups.

In summary, the results of the present study demonstrate that lifelong endurance training results in increased skeletal muscle lipid stores and shift toward greater numbers of oxidative fibers. While exercise metabolic efficiency was enhanced, older endurance trained subjects had lower glycogen and glycolytic fiber content, as well as a lower reliance on CHO-ox at moderate intensities. We conclude that these physiological adaptations to chronic aerobic training in older subjects may place them in an optimal position for moderate high-fat oxidation activity. Moreover, these data provide further evidence against triglyceride-mediated impairments in metabolic function. Conversely, the demonstration of higher muscle glycogen content in younger subjects supports the notion of a higher capacity for high-intensity training, supported by enhanced CHO-ox observed in this study. Our studies raise further questions on lifelong adaptations to exercise in terms of increased efficiency without modifying the balance between sources of substrate oxidation. Additionally, these data further emphasize the importance of chronic exercise throughout life to attenuate the deleterious effects of aging and sedentary lifestyle.

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J. J. D. researched data, contributed to the study concept, design and wrote the article. N. T. B. and A. D. researched the data. F. G. S. T. and M. S. R. performed the biopsies. B. H. G. contributed to the study concept, interpretation of the data and edited the article. F. A. researched the data, contributed to the study concept, design, analysis and interpretation of the data, and wrote the article.

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