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The mechanical and biochemical properties of tail tendon in a rat model of obesity: Effect of moderate exercise and prebiotic fibre supplementation

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ABSTRACT

The worldwide trajectory of increasing obesity rates is a major health problem precipitating a rise in the prevalence of a variety of co-morbidities and chronic diseases. Tendinopathy, in weight and non-weight bearing tendons, in individuals with overweight or obesity has been linked to metabolic dysfunction resulting from obesity. Exercise and dietary fibre supplementation (DFS) are common countermeasures to combat obesity and therefore it seems reasonable to assume that they might protect tendons from structural and mechanical damage in a diet-induced obesity (DIO) model. The purpose of this study was to determine the effects of a DIO, DIO combined with moderate exercise, DIO combined with DFS (prebiotic oligofructose), and DIO combined with moderate exercise and DFS on the mechanical and biochemical properties of the rat tail tendon. Twenty-four male Sprague-Dawley rats, fed a high-fat/high-sucrose diet were randomized into a sedentary, a moderate exercise, a DFS, or a moderate exercise combined with DFS group for 12 weeks. Additionally, six lean age-matched animals were included as a sedentary control group. DIO in combination with exercise alone and with exercise and DFS reduced the Young's Modulus but not the collagen content of the rat tail tendons compared to lean control animals. However, no differences in the mechanical and biochemical properties of the rat tail tendon were detected between the DIO and the lean control group, suggesting that DIO by itself did not impact the tail tendon. It seems that longer DIO exposure periods may be needed to develop overt differences in our DIO model.

1. Introduction

Obesity is associated with a variety of co-morbidities and chronic diseases, including cardiovascular disease (Nangia et al., 2016), impaired fasting glucose (Vaidya et al., 2016), cancer (Renehan et al., 2015; Soguel et al., 2016), and a variety of musculoskeletal diseases (Castro et al., 2016; Pottie et al., 2006; Stenholm et al., 2008).

Tendinopathy in obesity has gained special attention. Plantar fasciitis is a commonly observed tendinopathy in overweight and obese subjects, and has been linked to an increased stress on the passive structure of the foot due to overloading (Frey and Zamora, 2007; Irving et al., 2007). However, tendinopathies related to obesity have also been observed in non-weight bearing tendons such as the rotator cuff (Gumina et al., 2014) and elbow tendons (Titchener et al., 2013). Features associated with tendinopathy have also been reported in the tail tendon of obese animals. For example, the tail tendon in obese mice that were fed a high fat diet, was found to be softer than in lean mice (Eriksen et al., 2014). Additionally, ultrastructural analysis of the deep digital flexor

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tendon of rats showed differences in collagen fibril diameter distribution and mass-average diameter between obese (genetically obese (*fa/fa*) male Zucker rats) and lean (*Fa/Fa* or *Fa/fa* male Zucker rats) animals (Biancalana et al., 2010). These structural modifications affected the mechanical properties leading to a significant increase in maximum displacement and strain to failure in obese animals (Biancalana et al., 2010).

Tendon damage has been associated with metabolic disorders resulting from obesity (Abate et al., 2016; Castro et al., 2016). Adipose tissue releases bioactive peptides and hormones (e.g., cytokines, prostanoids, and metalloproteinases) (Coelho et al., 2013; Coppack, 2001; Guerre-Millo, 2002), which can influence tendon structure via activities on mesenchymal cells, leading to a systemic state of chronic, sub-clinical, low-grade inflammation that may damage tendons. Furthermore, cytokines released by visceral fat have been linked to tendon-bone health. Several pro-inflammatory cytokines are increased in animals with greater visceral fat, including interleukin-6 (IL-6), tumour necrosis factor alpha (TNFα), and C-reactive protein. TNFα has been reported to play a role in the production of pain and tendon pathology, and is thought to be a key cytokine in systemic spondyloarthropathy, a bone-tendon junction disease (Anttonen et al., 2006; Briot et al., 2005).

Sprague Dawley rats fed a high-fat/high-sucrose (HFS) diet are a well-established model of obesity. HFS fed rats have increased body fat and body mass, and have systemic inflammation and local inflammation within the knee (Collins et al., 2015c). Furthermore, HFS fed rats show structural changes in glycolytic skeletal muscles (Collins et al., 2016b; Collins et al., 2016c), and present with an increased rate of onset and progression of knee osteoarthritis (Collins et al., 2015c) compared to lean control animals fed a regular diet. Intramuscular fat invasion, fibrosis, and increased numbers of pro-inflammatory cells have been observed as rapidly as 3-days following the onset of a HFS diet (Collins et al., 2016c). However, tendinopathy has not been systematically studied in this model of obesity.

Exercise and dietary fibre supplementation are common countermeasures to combat obesity. Exercise reduces body fat (Donnelly et al., 2003; Jeffery et al., 2000), vascular inflammation (Pedersen, 2006; Pinto et al., 2012), brain inflammation (Chennaoui et al., 2015; Gomes da Silva et al., 2013), and systemic inflammation (Conti et al., 2015; Pedersen, 2006; Pinto et al., 2012). Furthermore, it has been suggested that physical activity provides protection against the detrimental effects of obesity on the musculoskeletal system. For example, four weeks of wheel-running exercise reduced the progression of osteoarthritis in obese mice fed a high-fat diet, and also disrupted the co-expression of pro-inflammatory cytokines (Griffin et al., 2012).

Similar to exercise interventions, dietary oligofructose fibre supplementation has been shown to attenuate increases in body fat, and is thought to improve metabolic health in a HFS diet rat model (Cluny et al., 2015; Parnell and Reimer, 2009), and has been shown to have beneficial effects in humans (Hume et al., 2015; Nicolucci et al., 2017). Therefore, it appears reasonable to assume that exercise and oligofructose interventions might protect tendons from structural and mechanical damage in a diet-induced obesity (DIO) model. However, this has never been shown.

Therefore, the purpose of this study was (1) to determine the effects of a HFS diet on the mechanical and biochemical properties of the rat tail tendon, and (2) to evaluate the effects of moderate exercise and fibre supplementation on the mechanical and biochemical properties of the tail tendon in adult rats fed a HFS diet. We hypothesized (1) that tendons of rats on a HFS diet have an increased content of collagen, and a higher failure strain compared to lean animals fed a regular diet, and (2) that exercise and fiber supplementation prevents the structural and mechanical changes induced by the HFS diet.

2. Methods

Thirty male, 10 to 12-week old Sprague Dawley rats, were housed individually and randomized into either a high-fat/high-sucrose (HFS, 20% of total weight as fat, 50% sucrose, 20% protein, and 10% from fibre and micronutrients; custom Diet #102412, Dyets, United States) diet-induced obesity group (HFS, n = 24) or a lean age-matched control group (standard chow low fat diet group – LFD, 5% of total weight as fat, 47.5% carbohydrates (only 4% from sucrose), 25% protein, 12.5% from fibre and micronutrients, and 10% moisture; Lab Diet 5001, United States, n = 6). Rats in the HFS group were divided into four subgroups: moderate exercise (DIO + E, n = 6), dietary fibre supplementation (DIO + F, n = 6), dietary fibre supplementation combined with moderate exercise (DIO + F + E, n = 6), and sedentary (DIO, n = 6). The moderate exercise intervention consisted of a progressive treadmill training program for 12 weeks, up to 30 min per day, 5 days a week (Rios et al., 2018); which corresponds to the recommended minimal physical activity guidelines in humans (de Souto Barreto, 2015). The fibre supplementation diet consisted of 10% oligofructose (Orafti P95, BENEO-Orafti, Germany) (Cluny et al., 2015). Four days following the intervention protocol, rats were lightly anaesthetized, body composition was measured via Dual X-ray absorptiometry (DXA), rats were then euthanized, and the tail harvested and frozen at −80 °C. Body mass was measured at the beginning of each week, and was normalized to the body mass measured in week one. All experiments were approved by the University of Calgary Life and Environmental Sciences Animal Care Committee, and all methods were conducted in accordance with the animal welfare regulations and guidelines at the University of Calgary.

2.1. Mechanical tests

On the day of mechanical testing, a tail was thawed at room temperature and individual tail tendons were dissected. Two tendons were tested from each tail. Dissected tendons were gripped by two clamps: one end was clamped to a load cell (100 N) of an MTS machine (Bionix, MTS Systems, Eden Prairie, MN, USA), the other end was clamped to the actuator piston for stretching of the tendon in a controlled manner. Tendons were irrigated with physiological saline and kept wrapped in a saline-saturated cloth between tests. Tendons were then stretched to a force of 1.5 N. The length, width and thickness in the middle, and at the proximal and distal ends of the tendon were measured using calipers. Following a preconditioning protocol consisting of twenty stretch-shortening cycles of 0.5% strain at a speed of 2.5% strain per minute, tendons were subjected to two stress-relaxation tests. The stress-relaxation tests consisted of a stretch of 2% and 3% strain at a speed of 10% and 15% strain per minute, respectively. The tendon was then allowed to stress-relax for 2 min at the final length. The tendon was then stretched to failure at a constant speed of 12% strain/minute. Following the mechanical testing, tendons were kept at −80 °C until hydroxyproline content determination.

Stress (σ) was calculated by dividing the force by the cross-sectional area, assuming that the tendon has a rectangular cross sectional shape (Seto et al., 2009). The peak stress obtained during stretching, the steady-state stress after stress-relaxation, the maximal stress and strain, the yield stress and strain, and the Young's modulus (Fig. 1) were compared between groups. All mechanical tests were performed within three months of harvest.

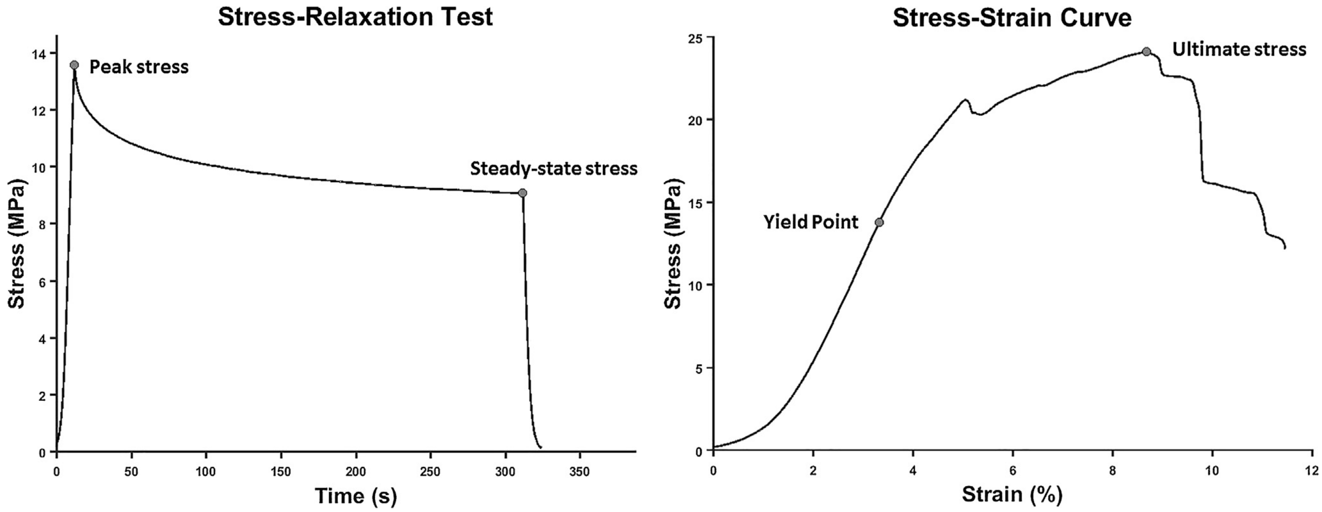

Fig. 1. Stress-relaxation (left) and stress-strain (right) graphs from one representative tail tendon. Tendons were stretched to a force of 1.5 N. Following a preconditioning protocol consisting of twenty stretch-shortening cycles of 0.5% strain at a speed of 2.5% strain per minute, tendons were subjected to two stress-relaxation tests. The stress-relaxation tests consisted of a stretch of 2% and 3% strain at a speed of 10% and 15% strain per minute, respectively. The yield point was defined as the point when the slope decreases by one unit from the maximum slope.

2.2. Hydroxyproline (Collagen) content

Tendons were powdered using a cooled crusher in liquid nitrogen and lyophilized for 24 h under vacuum. Lyophilized tendons were then incubated with 6 N HCl for 18 h at 105 °C for hydrolysis. Samples were then cooled at room temperature, centrifuged, and hydroxyproline concentration was determined according to a colorimetric method (Woessner 1961) using 4-(Dimethylamino) benzaldehyde (Sigma Aldrich, hydroxyproline assay kit, MAK008).

2.3. Statistical analysis

Kruskal-Wallis test was used to assess differences between groups for all variables (body mass, body fat, and mechanical and biochemical properties). If significant ($p < 0.05$), post hoc Mann-Whitney U-Test was used to indicate which groups differed. Body mass was normalized by that measured at week 1 of the experimental protocol and expressed as a percent change in body mass.

3. Results

3.1. Body mass

Body mass increased for all groups of rats during the experimental period. Body mass increased less in LFD, DIO + E, and DIO + F + E group rats compared to DIO group rats, starting from week 3 of the experimental protocol ($p < 0.05$, Fig. 2). While rats in the DIO + F group exhibited a trend towards a reduced increase in body mass compared to DIO animals, starting at week 3 of the experimental protocol ($p < 0.10$), this difference only became statistically significant ($p < 0.05$) in week 9 (Fig. 2).

3.2. Body fat composition

DIO, DIO + E, and DIO + F group rats had 16%, 7%, and 8% more body fat than LFD group rats ($p < 0.05$), respectively. DIO + E + F group rats had the same percentage of body fat as the LFD group rats, and a lower percentage of body fat than the DIO, DIO + E, and DIO + F group rats ($p < 0.05$, Fig. 3).

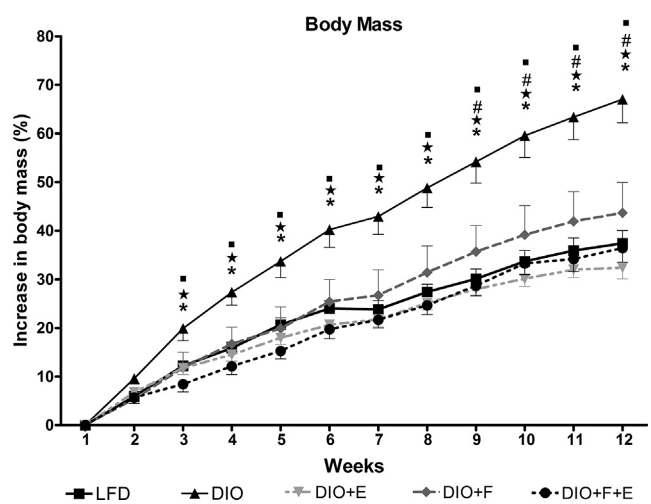

Fig. 2. Mean (±1 SE) percent increase in body mass from the body mass measured in week 1. * indicates a significant difference from LFD group rats. ★ indicates a significant difference from DIO + E group rats. # indicates a significant difference from DIO + F group rats. ■ indicates a significant difference from DIO + F + E group rats. LFD: low fat diet group; DIO: diet induced-obesity group; DIO + E: diet induced-obesity combined with moderate exercise group; DIO + F: diet induced-obesity combined with fiber supplementation group; DIO + F + E: diet induced-obesity combined with fiber supplementation and exercise group.

3.3. Mechanical and biochemical properties of tail tendons

Steady-state and peak stresses in the 2% and 3% stress relaxation tests were similar between experimental groups (Fig. 4), as were the maximal stress, maximal strain, yield stress and yield strain in the failure test protocol (Fig. 5). The Young's modulus was the same in LFD and DIO group rats, while the Young's modulus was smaller in DIO + E and DIO + E + F than LFD group rats ($p = 0.002$ and $p < 0.000$, respectively; Fig. 6). Hydroxyproline content was similar across groups (Fig. 7).

4. Discussion

The main findings of this study were that (1) DIO and DIO combined with fibre supplementation did not alter the mechanical and

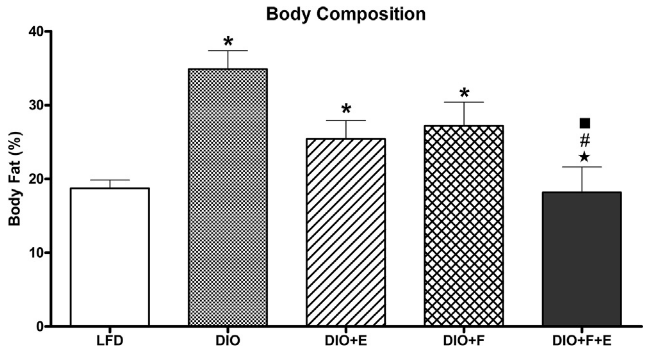

Fig. 3. Mean (+1 SE) percent body fat measured at the end of the experimental protocol. *indicates a significant difference from LFD group rats. ■ indicates a significant difference from DIO group rats. ★ indicates a significant difference from DIO + E group rats. # indicates a significant difference from DIO + F group rats. LFD: low fat diet group; DIO: diet induced-obesity group; DIO + E: diet induced-obesity combined with moderate exercise group; DIO + F: diet induced-obesity combined with fiber supplementation group; DIO + F + E: diet induced-obesity combined with fiber supplementation and exercise group.

biochemical properties of the rat tail tendons and that (2) DIO combined with moderate exercise, and DIO combined with exercise and fibre supplementation reduced the elastic modulus, but not the collagen content of the tail tendon in rats when compared to LFD rats.

There is a significant positive association between musculoskeletal disorders and the level of obesity (Kortt and Baldry, 2002). Knee, hip and hand osteoarthritis, low back pain, diffuse idiopathic skeletal hyperostosis, carpal tunnel syndrome, plantar fasciitis, osteoporosis, rheumatoid arthritis, and fibromyalgia are some examples of these disorders (Anandacoomarasamy et al., 2008). Specifically, tendinopathy has received focussed attention due to its high incidence rate in subjects with obesity compared to non-obese subjects (Albers et al., 2016; de Jonge et al., 2011).

Mice, and Sprague Dawley and Wistar rats fed with a high-fat/high-sucrose (HFS) diet are a well-established model of diet-induced obesity (Collins et al., 2016c; Collins et al., 2015c; Lorincz et al., 2010; Rosas-Villegas et al., 2017), and have been found to have increased systemic and local inflammation in the knee of Sprague Dawley rats (Collins et al., 2015c). Furthermore, a HFS diet has been shown to result in metabolic disorders in rats and mice, compromising skeletal muscle structure and function, and knee cartilage, meniscus, and bone integrity (Collins et al., 2016c; Collins et al., 2015c; Lorincz et al., 2010; Rios et al., 2019).

Contrary to our hypothesis, and in spite of being a well-established model for musculoskeletal disorder (Collins et al., 2016a; Collins et al., 2015a; Collins et al., 2016c; Collins et al., 2015b; Collins et al., 2015c; Rios et al., 2019), the HFS diet does not appear to affect the mechanical and biochemical properties of rat tail tendons after 12 weeks on diet, and thus, diet-induced alterations to tendon integrity appears to follow a different time course than those other components of the musculoskeletal system. This result does not agree with previous studies showing alterations in the mechanical and structural properties of tail tendons of obese animals. There are a few possible explanations that may account for this discrepancy between our results and those obtained by others.

Tendinopathies in tail tendons of rats and mice have typically been found at time points greater than the 12 week period used in this study. For example, Eriksen et al. (2014) found a 13% decrease in plateau modulus and a 12% decrease in total modulus in mice fed with a high-fat diet for 32 weeks compared with mice fed a chow diet (Eriksen et al., 2014). In the model used in this study, an induction period of 10–12 weeks is typically required for animals to reach "heterostasis" and demonstrate increased mass and increased metabolic disorders (Collins et al., 2015c; Rios et al., 2019). Thus, it seems that although a 10–12 week period protocol of HFS diet is sufficient to induce increases in body mass and body fat, it is not enough to alter the mechanical and biochemical properties of the tail tendons, but might have affected other tendons, for example, weight bearing tendons (not evaluated in the present studies). Similar results were obtained by David et al. (2014) who found no differences in tendon mechanical properties in mice after 12 weeks on a high-fat diet. Carroll et al. (2006) and Silva et al. (2014) did not find changes in cardiac collagen content at 12–15 weeks of obesity induction between lean and obese rats, supporting our findings in tail tendons.

Previous studies have reported model-specific adaptations to obesity in animals. It has been suggested that there are differences between models of obesity and associated effects on musculoskeletal

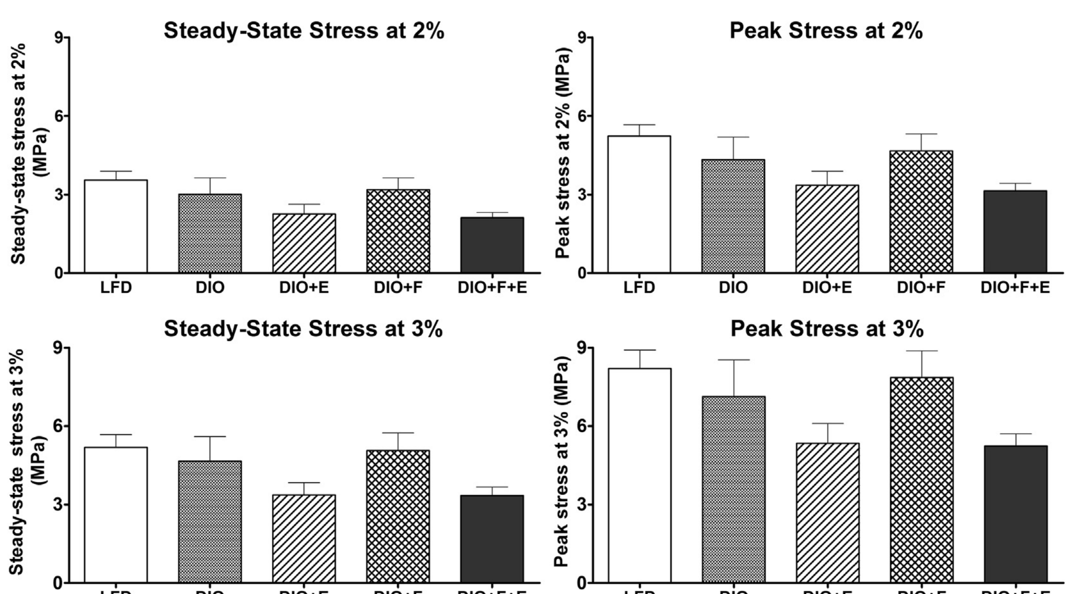

Fig. 4. Mean (+1 SE) static and dynamic stress at 2% and 3%. There was no difference between groups for the steady-state and peak stress at either 2% and 3%. LFD: low fat diet group; DIO: diet induced-obesity group; DIO + E: diet induced-obesity combined with moderate exercise group; DIO + F: diet induced-obesity combined with fiber supplementation group; DIO + F + E: diet induced-obesity combined with fiber supplementation and exercise group.

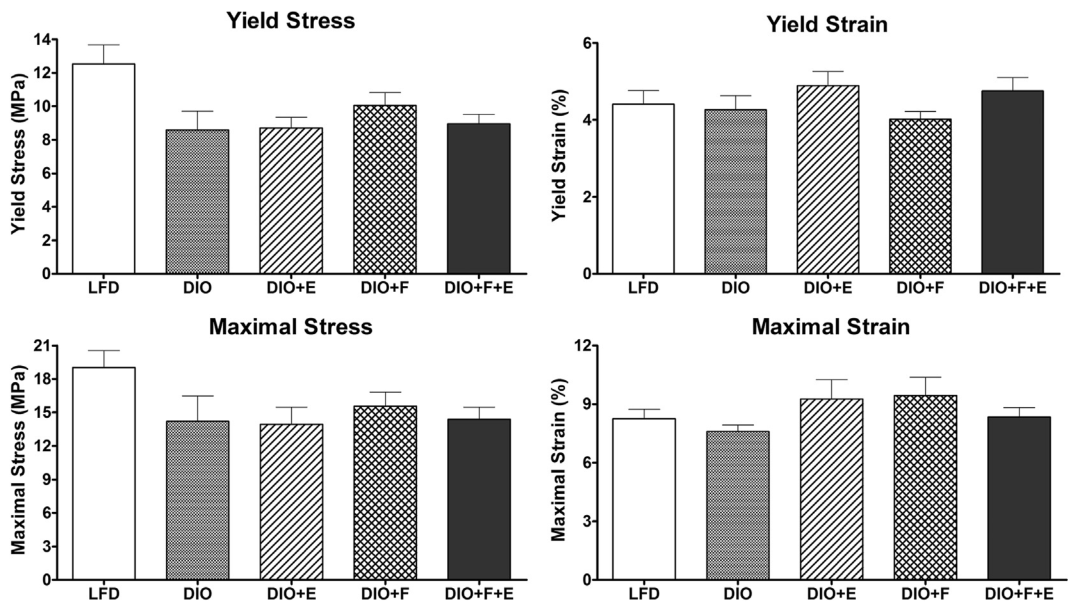

Fig. 5. Mean (+1 SE) yield stress and strain (top), maximal stress and strain (bottom). There was no difference between groups for yield stress, yield strain, maximal stress, and maximal strain. LFD: low fat diet group; DIO: diet induced-obesity group; DIO + E: diet induced-obesity combined with moderate exercise group; DIO + F: diet induced-obesity combined with fiber supplementation group; DIO + F + E: diet induced-obesity combined with fiber supplementation and exercise group.

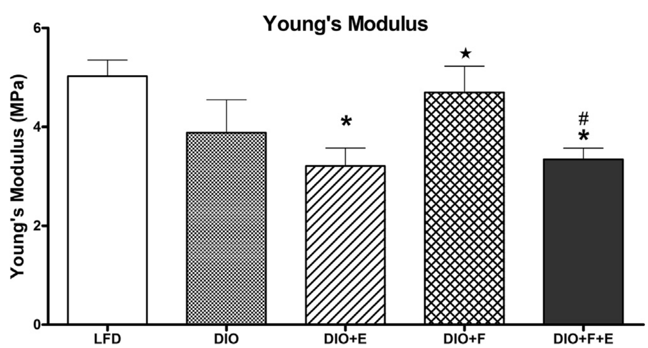

Fig. 6. Mean (+1 SE) Young's Modulus. * indicates differences from LFD group rats. ★ indicates difference from DIO + E group rats. # indicates difference from DIO + F group rats. LFD: low fat diet group; DIO: diet induced-obesity group; DIO + E: diet induced-obesity combined with moderate exercise group; DIO + F: diet induced-obesity combined with fiber supplementation group; DIO + F + E: diet induced-obesity combined with fiber supplementation and exercise group.

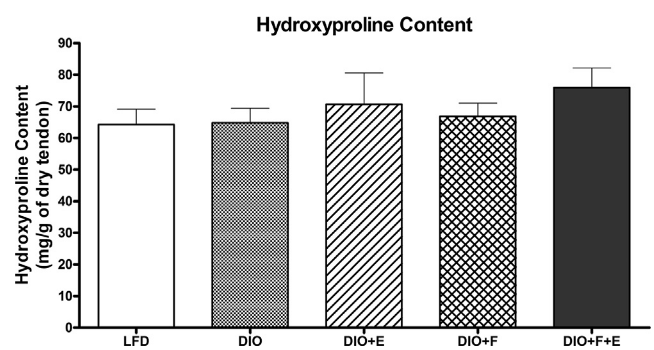

Fig. 7. Mean (+1 SE) hydroxyproline content. LFD: low fat diet group; DIO: diet induced-obesity group; DIO + E: diet induced-obesity combined with moderate exercise group; DIO + F: diet induced-obesity combined with fiber supplementation group; DIO + F + E: diet induced-obesity combined with fiber supplementation and exercise group.

tissues (Li et al., 2008). Tendon mechanical and biochemical alterations have been observed in the monogenic Zucker rat model of obesity compared to control (Biancalana et al., 2010). Genetically obese Zucker rats bear a mutation in the leptin receptor gene (Phillips et al., 1996), thus the changes in tendon properties might be related to the leptin receptor deficiency rather than the obesity itself.

Aging affects the mechanical properties of tendons and the turnover rate of collagen fibres from tail tendons (Everitt et al., 1980; Everitt et al., 1983). Therefore, the age of the animals may influence tendon adaptations in models of obesity and metabolic disorder. Tendons from old animals compared to young have increased stiffness, increased elastic modulus, increased peak tension (Wood et al., 2011), and the collagen turnover rate is up to 30 times lower (Karsdal et al., 2016). Our rats were 23–25 weeks old when tissue was collected, while in comparable studies, tail tendons were harvested at an older age, for example, at 40 weeks of age by Eriksen et al. (2014). Therefore, our relatively young animals might have had a greater potential to renew collagen, which might also have inhibited the onset of the detrimental effects of obesity on the tendons of our animals compared to the older animals used in previous studies.

However, the HFS diet combined with exercise was associated with a reduction in the Young's modulus of the tail tendon compared to that obtained in LFD control animals. Exercise in normal weight animals has beneficial effects on tendon morphology and function (Kubo et al., 2001; Langberg et al., 2001; Langberg et al., 1999; Narici et al., 1996). It has been shown that chronic exercise induces collagen fiber formation (Langberg et al., 2001; Langberg et al., 1999), and an increased cross sectional area and stiffness in weight bearing tendons of humans (Kubo et al., 2001; Narici et al., 1996), horses (Birch et al., 1999), and pigs (Woo et al., 1981). However, little is known about the effects of chronic exercise on non-weight bearing tendons in young and old animals. Viidik et al. (1996) reported a decrease in tail tendon Young's modulus in older animals as we observed here in the present study (Viidik et al., 1996). But the mechanism behind this change is not well understood. In the current study we did not evaluate the effects of exercise and/or prebiotic fibre on tendons in chow fed rats, therefore we cannot provide a direct evidence on the effects of exercise or prebiotic fibre on tendons in normal weight animals. This is a limitation of our study.

In this study, exercise prevented weight and fat gains typically associated with HFS diets, and was associated with a decrease in the Young's modulus in tail tendons without modifying its collagen content when compared to LFD rats. The lack of correlation between the Young's modulus and collagen has been found before (Oxlund, 1980), since the Young's modulus is also determined by the structural arrangement of collagen and the cross-linking between collagen fibres (Depalle et al., 2015; Guthold et al., 2007). The reduction in Young's modulus in our DIO + E and DIO + E + F rats could be due to changes in cross linking between collagen fibres and their size and structural arrangement within the tail tendon (Biancalana et al., 2010; Derwin and Soslowsky, 1999). However, it is not clear whether the reduction in Young's modulus is beneficial or a sign of degeneration in non-weight bearing tendons.

Dietary modulation may protect against metabolic disease. Previous studies have shown that a dietary fibre intervention was effective in reducing body mass and in increasing metabolic health in rats (Rios et al., 2019; Cluny et al., 2015), and humans (Nicolucci et al., 2017; Hume et al., 2015; Parnell and Reimer, 2009). A HFS diet combined with fibre supplementation did not show a difference in the mechanical and biochemical properties of the rat tail tendon compared to either the LFD or the DIO groups, suggesting that either there is no effect of this intervention or a longer period of exposure is required to observe the effects. Further studies with longer periods of exposure to the DIO, exercise, and fibre supplementation than used here, and chow fed animals subjected to exercise and fibre supplementation may be needed to help understand the systemic effect of obesity, exercise, and fibre supplementation on the non- weight bearing tendons of animals exposed to a HFS diet.

5. Conclusion

DIO and DIO combined with fibre supplementation did not lead to detectable differences in the mechanical and biochemical properties of the rat tail tendon compared to LFD rats. However, DIO combined with moderate exercise, and DIO combined with moderate exercise and fibre supplementation reduced the Young's modulus when compared to LFD rats, but not the collagen content of the tail tendon in rats. Based on these results, a high-fat/high-sucrose diet by itself has no effect on tail tendon. Longer periods of exposure to the high-fat/high-sucrose diet, may be needed to alter the mechanical and biochemical properties of non-weight bearing tendons.

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Conflict of Interest

Jaqueline L. Rios, Loretta Ko, Venus Joumaa, Shuyue Liu, Fernando Diefenthaeler, Andrew Sawatsky, David A. Hart, Raylene A. Reimer, and Walter Herzog have no conflict of interest.

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