Could leptin-deficient mice be good novel models for diabetic Achilles tendinopathy?

Sirs,

We have read with great interest the article entitled "Pathologic changes of Achilles tendon in leptin-deficient mice" published in *Rheumatology International*. In this study, Ji *et al*. demonstrated the histopathological changes of Achilles tendon in leptin-deficient mice, supporting that diabetic foot is initiated by increased passive stiffness within the gastrocnemius-soleus musculotendinous unit (1). Moreover, this interesing paper indicated that ob mice are good new models to investigate the process of diabetic Achilles tendinopathy. However, we have several concerns about this study.

It has been generally accepted that overuse conditions play an essential role in the pathogenesis of Achilles tendinopathy (2). Ob mice have not only been recommended as the diabetes model, but also the classic animal model of obesity, The body weight of ob mice with C57BL/6J background is approximately two or three times greater than the wild type mice in the twelve weeks after birth (3). In addition, obesity has been recognised as the independent risk factor of Achilles tendinopathy in human beings (4, 5). Therefore, the excess body weight of ob mice should be taken into consideration in the pathogenesis of Achilles tendinopathy. Obesity leading to the overload on normal Achilles tendon may be detrimental to the balance of micro-repair and microtrauma intra Achilles tendon. The trend to spontaneous rupture of Achilles tendon in ob mice may be due to the overuse conditions caused by obesity, according to recent animal model studies (6, 7).

Since it has been suggested that higher serum leptin concentration in obesity and type 2 diabetes patients indicates leptin resistance (8, 9), leptin deficiency in ob mice may not represent the changes of decompensated leptin signalling during the diabetic Achilles tendinopathy development. It has been proposed that type 2 diabetes may compromise Achilles tendon healing by decreasing the degradation of matrix proteins and impairing tissue remodelling (10). Further study indicated that experimental diabetes could influence the homeostatic imbalance of tendons and, consequently, lead to the notable structural, inflammatory and vascular changes in the rat Achilles tendon (11). Therefore, more attention should be paid to the effect of impaired leptin signalling in ob mice on the Achilles tendon homeostasis. We could speculate that the lack of leptin may accelerate the degeneration of the Achilles tendon from the results of Ji *et al*., which implied that leptin signalling may be involved in the tendon regeneration process. The question whether leptin resumption by fat transplantation in ob mice could rescue or delay the pathogenesis of Achilles tendinopathy may gain popularity in future research.

Moreover, since the role of neuropathy in the diabetic Achilles tendinopathy development has not been fully understood and the neuroprotection effect of leptin has been revealed only recently (12), the potential effect of leptin signalling on neuropathy for diabetic Achilles tendinopathy prevention should consequently arouse more interest. The leptin-deficient ob mice and the leptin receptor mutation db mice could be powerful animal models for further research.

In summary, we believe that the study of Ji *et al*. will lead to further investigations concerning ob mice as a useful model for diabetic Achilles tendinopathy. But it should obviously be kept in mind that obesity will be the confounding factor in this model. Further focuses are still needed to clarify the potential role of leptin signalling in diabetic Achilles tendinopathy.

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