European Journal of Orthopaedic Surgery & Traumatology (2019) 29:697–703
https://doi.org/10.1007/s00590-018-2336-2

ORIGINAL ARTICLE • ANKLE - GENERAL ORTHOPAEDICS

Mid-portion Achilles tendinopathy in runners with metabolic disorders

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Received: 15 August 2018 / Accepted: 22 October 2018 / Published online: 26 October 2018

Abstract

Introduction Running is a very popular modality of physical activity, which may help to lose weight and normalize pathological values of blood parameters in subjects suffering from metabolic disorders. Given that both overuse and metabolic pathologies are responsible for the onset of tendon damage, aim of the present study was to evaluate whether the first group of pathogenetic factors or the latter was more responsible for mid-portion Achilles tendinopathy.

Method Thirty-six and 28 subjects with and without mid-portion Achilles tendinopathy, who were regular runners and started running for metabolic disorders, were enrolled, respectively. Information about body weight and blood parameters at baseline was collected. The characteristics of running practice, dietary habits and anthropometric measures were registered. An ultrasound evaluation of the tendon was performed, and the blood metabolic parameters were evaluated.

Results The amount of running years and mileage was equivalent in both groups. A similar weight loss was observed; the subjects with mid-portion Achilles tendinopathy showed a worse metabolic profile (Hb1aC%, $p=0.008$; total cholesterol, $p=0.04$; HDL cholesterol, $p=0.003$; triglycerides, $p=0.009$).

Conclusions These findings suggest that the subjects with less evident positive effects of running on metabolism are more exposed to the onset of mid-portion Achilles tendinopathy.

Keywords Achilles tendon · Metabolism · Overweight · Running

Introduction

Running is a very popular modality of physical activity, practiced by many individuals to improve cardio-respiratory function and general well-being [1]. Several people, suffering from metabolic disorders (obesity, diabetes, glucose intolerance, hypercholesterolemia and/or hypertriglyceridemia), run in the attempt to lose weight and normalize pathological values of blood parameters [2].

Mid-portion Achilles tendinopathy (mAT) is a frequent running-related injury which occurs in 6–12% of subjects [3]. Several factors interact in the pathogenesis: number of running years, distance and speed, weekly running distance, training errors (i.e., rapidly increasing training intensity or duration) [4] and a genetic predisposition [5]. Moreover, the same metabolic disorders that are efficaciously counteracted by running have been found frequently associated with mAT [6]. However, to our knowledge, it is unknown whether the first group of pathogenetic factors (running characteristics) or the latter (metabolic disorders) are more responsible for this tendinopathy.

Aim of the present study was to evaluate the factors pertinent to running modalities (frequency of sessions, running distance) and to the subject (demographic, anthropometric and biochemical parameters) possibly associated with the onset of mAT in runners with metabolic disorders.

Materials and methods

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included prior to their inclusion in the study.

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Institutional ethics committee approval was not required for the nature of this study [7].

Runners with mAT were selected. The diagnosis was made on the basis of medical history, clinical examination (pain, tenderness and/or functional limitation) and ultrasound (US) and color Doppler (CD) features of tendon damage. Runners were defined subjects who ran at least ≥ 3 times/week, only persons who at least ran 10 km for week, and cumulatively 9 months/year were taken into account. Occasional and novice runners (persons who did not run on a regular basis for the past year) were excluded.

All the subjects were administered a structured questionnaire evaluating their running practice and medical history. Namely, besides the years of practice, information referred to the last year was obtained on kilometers ran/week, annual kilometers, running speed (km/h), number of sessions/week and cumulatively. Other sport activities (regular or occasional) were also recorded. Participants were asked about the original motivation with particular reference to overweight and metabolic disorders. Body weight at the beginning of running practice was obtained. Medical records were collected when available, and the use of drugs was registered.

Only the subjects who were regular runners and who started running because of overweight/obesity and/or abnormal values of metabolic parameters were included in the study group.

A control group was formed enrolling volunteers who started running for the same health motivations.

In each subject, height and weight were measured. BMI and waist/hip (W/H) ratio were calculated. Overweight and obesity were diagnosed when BMI was > 25 or > 30, respectively. Blood pressure was taken at rest, three times at a 5-min interval, and the mean of these measurements was computed. Hypertension was diagnosed for values of systolic blood pressure > 140 mm Hg and of diastolic blood pressure > 90 mm Hg. A dietary inquiry was performed, using the dietary screener questionnaire, which is available for public use. On the basis of data collected, the caloric intake was calculated and judged low/high or adequate in relationship to the energetic expenditure of each person according to age, sex, work and sport activities [8]. Blood was collected to measure glycated hemoglobin (Hb1aC), triglycerides, total cholesterol and HDL cholesterol.

In the subjects with mAT, pain and function were measured by means of Victorian Institute of Sport Assessment—Achilles (VISA-A) questionnaire (adapted to the Italian language) [9]. Therefore, all participants underwent an US evaluation, using a high-resolution, multi-frequency (6–15 MHz) linear array transducer (*ProSound ALPHA10, Aloka, Japan*). Both longitudinal and transverse scans were taken with the patient lying prone, with the feet hanging over the edge of the table at 90° of flexion [10]. The presence of dishomogeneous hypo- or hyperechoic thickening, diffuse or focal, of the tendon, associated with loss of the normal fibrillar pattern and/or irregularity of the tendon margins, was interpreted as a sign of degeneration. On the basis of these structural abnormalities, tendons were then stratified for severity as "mild" (one area of disorganized echotexture, i.e., focal dishomogeneous area with loss of fibrillar pattern), "moderate" (some areas of disorganized echotexture, i.e., dishomogeneous hypo- or hyperechoic tendon damage with altered fibrillar pattern) and "severe" (diffuse disorganized echotexture and hypo- or hyperechoic areas with irregularity of tendon margins and/or calcifications) [11]. The presence of neovascularization was investigated by means of CD and graded as (0), (1+), (2+) and (3+) according to a semiquantitative estimate of the number of vessels. When no vessels were visible, the estimation was 0. When there were one or two small vessels mostly in the anterior part of the tendon, the estimation was (+1). When there were several irregular vessels throughout the tendon, the estimation was (+2) to (+4) [12].

Results

Out of 144 patients with mAT, 36 were regular runners with metabolic disorders and met inclusion criteria. VISA-A score was 46.5 ± 9 in males and 45.1 ± 7.2 in females. Abnormal echostructural features were seen in all the subjects with mAT (13 mild, 13 moderate and 10 severe) (Fig. 1). CD examination showed grades (0), (+1), (+2), (+3) and (+4) in 8, 10, 9, 7 and 2 subjects, respectively. Twenty-eight subjects with the same characteristics without mAT formed the control group.

In Table 1, demographic data and anthropometric features of participants at baseline are reported. The subjects of the study and control group did not differ for age, sex and anthropometric measures. The percentage of those who started running because of overweight/obesity was equivalent in males and females.

In Table 2, data on metabolic disorders at baseline are included. In the study group, these data were obtained from medical records in 20 subjects and verbally in 6 subjects (totally 26 subjects) and in the control group in 10 and 4 subjects (totally 14 subjects), respectively. Ten and 14 subjects in each group did not perform blood tests and started running exclusively to lose weight. All the differences were not statistically significant.

Similarly, no significant difference was registered in the running characteristics (Table 3): Years of practice, sessions and kilometers run were equivalent in study and control groups. As expected, number of sessions, kilometers run and running speed were higher in males.

In Table 4, anthropometric parameters are shown. In both groups, positive effects of running were noticed: In

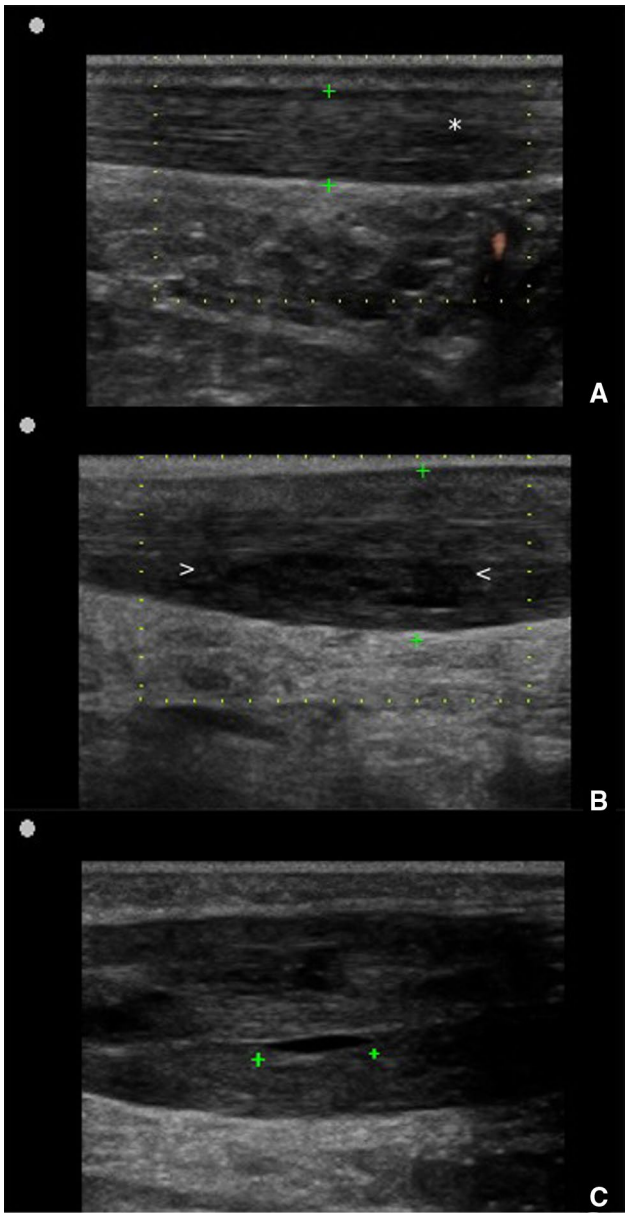

Fig. 1 US appearance of tendon damage. In panel A (mild abnormalities), only one area of disorganized echotexture (focal dishomogeneous area with loss of fibrillar pattern [*]) is seen. Tendon margins are regular (calipers). In panel B, moderate damage, characterized by some hypo- or hyperechoic areas of altered fibrillar pattern, especially in the ventral portion of the tendon (arrowheads), can be observed; moreover, the tendon is thickened and its margins are irregular (calipers). In panel C, severe tendon abnormalities are present. In particular, a diffuse disorganized echotexture and hypo- or hyperechoic areas with irregularity of tendon margins are seen. An intratendinous partial lesion (anechoic area between calipers) can be also observed

comparison with baseline values, an evident weight loss and a reduction in BMI values were observed both in mAT group (from 26.9 ± 2.8 to 25.1 ± 2.4, $p = 0.002$) and in control group (from 26.2 ± 2.6 to 24.3 ± 1.7, $p = 0.001$); accordingly, the percentage of subjects overweight and obese was reduced (from 24/36 to 18/36, $p = 0.15$ and from 18/28 to 11/28, $p = 0.06$, respectively).

However, despite the similar weight loss, the patients with mAT were characterized by a worse metabolic profile. Indeed, in this group the mean values of Hb1aC, total cholesterol and triglycerides were significantly higher, and on the contrary the values of HDL cholesterol were lower (Table 5). The percentage of subjects with abnormal metabolic parameters, which was equivalent in both groups at baseline (Table 2), decreased more in those without mAT than in those with mAT (4/28 vs 12/36; $p = 0.08$).

Discussion

Running is a very popular modality of physical activity, which may help to lose weight and normalize pathological values of blood parameters, in subjects suffering from metabolic disorders (obesity, diabetes, glucose intolerance, hypercholesterolemia and/or hypertriglyceridemia) [2]. However, lower limbs injuries are frequent in runners. The medial tibial stress syndrome is most common, followed by patellofemoral pain, medial meniscal damage, AT and plantar fasciitis [3]. Among these injuries, AT is one of the more important for prevalence and clinical impact, because it is often recalcitrant to treatments and may compromise the further practice of sport activities [13].

Overuse is a well-recognized risk factor for AT. Mechanical loading is essential to maintain tendon homeostasis, but when the individual threshold of loading frequency and magnitude is overcome, the tendon response reverses from beneficial toward degenerative. In runners, the number of running years, kilometers run, speed, training errors (i.e., rapidly increasing training intensity or duration) and a genetic predisposition [5] are considered relevant risk factors. Between the sexes, males are most at risk by a factor of 2:1 to 12:1 to their female counterparts [14].

Besides overuse, the importance of metabolic disorders has been emphasized. Epidemiological data show an increased prevalence of diabetes in subjects with tendinopathy compared to controls without tendinopathy and conversely a higher prevalence of tendinopathy in subjects with diabetes compared to controls without diabetes [6]. An increased Achilles tendon thickness and US degenerative features, as well as an increased plantar fascia thickness, have been reported in patients with diabetes, mainly in those complicated by neuropathy [15]. According to an accepted hypothesis, tendon damage in diabetes is caused by an excess of advanced glycation end products, which form a covalent cross-link within collagen fibers, altering their structure and functionality [15]. Similarly, most patients with heterozygous familial hypercholesterolemia develop Achilles tendon xanthoma, and people

Table 1 Demographic and anthropometric features of participants at baseline

	Study group	Controls	*p*	Study group		*p*	Controls		*p*
	All	All		Males	Females		Males	Females	
Number	36	28		22	14		18	10	
Age	39.3 ± 12.9	39.1 ± 11.6	0.47	40.4 ± 12.6	37.7 ± 13.5	0.27	39.5 ± 11.8	38.6 ± 11.9	0.42
Height	169 ± 7.6	170.7 ± 8.4	0.28	173.7 ± 4.8	163.1 ± 6.6	0.0001	174.7 ± 18	163.7 ± 7.49	0.0001
Weight	77.6 ± 9.8	76.6 ± 9.5	0.33	81.9 ± 9.4	70.9 ± 6.2	0.0001	80.1 ± 9.3	70.2 ± 6.1	0.002
BMI									
Mean	26.9 ± 2.8	26.2 ± 2.6	0.16	27 ± 2.9	26.6 ± 2.7	0.33	26.2 ± 2.8	26.2 ± 2.3	0.49
Overweight	20/36 (55.5%)	16/28 (57.1%)	0.89	12/22 (54.5%)	8/14 (57.1%)	0.87	9/18 (50%)	7/10 (70%)	0.30
Obesity	4/36 (11.1%)	2/28 (7.1%)	0.58	3/22 (13.6%)	1/14 (7.1%)	0.54	2/18 (11.1%)	0	

Table 2 Metabolic disorders and hypertension at baseline

	Study group			Controls		
	All	Males	Females	All	Males	Females
Number	26	16	10	14	8	6
Pathologies						
Diabetes	4 (15.3%)*	3 (18.7%)	1 (10%)	3 (21.4%)*	2 (25%)	1 (16.6%)
Impaired fasting glucose	11 (42.3%)	7 (43.7%)	4 (40%)	4 (28.5%)	2 (25%)	2 (33.3%)
Abnormal lipid profile	11 (42.3%)	9 (56.2%)	3 (30%)	5 (35.7%)	4 (50%)	1 (16.6%)
High blood pressure	7 (26.9%)	5 (31.2%)	4 (40%)	6 (42.8%)	4 (50%)	2 (33.3%)
Drugs						
Antidiabetic	4 (15.3%)	3 (18.7%)	1 (10%)	3 (21.4%)	2 (25%)	1 (16.6%)
Lipid lowering	2 (7.6%)	2 (12.5%)	0	2 (14.2%)	1 (12.5%)	1 (16.6%)
Antihypertensive	4 (15.3%)	2 (12.5%)	2 (25%)	2 (14.2%)	2 (25%)	0

Ten subjects in the study group and 14 subjects in the control group did not perform blood test and started running to lose weight

In the study group, 18/26 subjects were obese/overweight (5/14 in the controls)

*Two patients (1 male and 1 female) and one patient (male) with diabetes in the study and control groups, respectively, were obese/overweight and showed an abnormal lipid profile

Table 3 Running parameters

	Study groups	Controls	*p*	Study group		*p*	Controls		*p*
Subjects	All	All		Males	Females		Males	Females	
Years of practice	4.1 ± 1.4	4.1 ± 1.3	0.40	3.8 ± 1.2	4.7 ± 1.6	0.04	4.1 ± 1.5	4 ± 1.1	0.38
Sessions									
× Week	2.9 ± 1	3 ± 1.1	0.36	3.2 ± 1.2	2.5 ± 0.6	0.01	3.2 ± 1	2.7 ± 1.3	0.11
× Year	121 ± 44.2	124.5 ± 46.2	0.37	133.8 ± 48.4	100.8 ± 27.4	0.01	133.5 ± 41.8	108.4 ± 51.4	0.08
km ran									
× Week	22.3 ± 6.3	23.8 ± 6.4	0.17	24 ± 6.8	19.6 ± 4.4	0.02	25.3 ± 6.6	21 ± 5.2	0.04
× Year	1017.2 ± 331.4	1087.4 ± 272.6	0.18	1105.6 ± 372.9	878.4 ± 192.5	0.02	1162.6 ± 279	952.2 ± 210.5	0.02
Running speed (km× h)	9.7 ± 2	10.7 ± 2.4	0.04	10.3 ± 2.1	8.9 ± 1.6	0.02	11.2 ± 2.7	9.8 ± 1.6	0.06
Other sports	9	9		6	3		7	2	

with non-familial hypercholesterolemia show damaged tendon tissues, probably because of microscopic cholesterol deposition and a low-grade persistent inflammation [6]. Finally, overweight and obesity are strong risk factors for AT, either for the increased yield on the tendon or for the biochemical alterations due to the frequent association of dysmetabolic conditions (both impaired glucose and

Table 4 Anthropometric parameters

	Study group	Controls	*p*	Study group		*p*	Controls		*p*
	All	All		Males	Females		Males	Females	
Number	36	28		22	14		18	10	
Weight loss	5.1 ± 3.4	5.3 ± 3.6	0.41	4.7 ± 3.3	5.7 ± 3.5	0.19	5.1 ± 3.7	5.8 ± 3.4	0.31
BMI									
Mean	25.1 ± 2.4	24.3 ± 1.7	0.82	25.4 ± 2.2	24.5 ± 2.5	0.12	24.5 ± 1.9	24 ± 1.5	0.23
Overweight	18	11	0.39	13	5	0.17	8	3	0.4
Obesity	0	0		0	0		0	0	
W/H ratio	96 ± 9	94.6 ± 10.4	0.29	100.2 ± 7.2	89.2 ± 7.6	0.0000	99.3 ± 8.1	86.2 ± 8,8	0.0002
Out of normal range*	16	10	0.4	10	6	0.8	6	4	0.7

*Men > 102, women > 88

Table 5 Metabolic parameters, drugs and caloric intake

	Study group	Controls	*p*	Study group		*p*	Controls		*p*
	All	All		Males	Females		Males	Females	
Number	36	28		22	14		18	10	
Hb1aC (%)	5.7 ± 1	5.2 ± 0.5	0.008	5.8 ± 1.1	5.6 ± 0.8	0.32	5.3 ± 0.6	5 ± 0.3	0.15
> 5.7	11	3	0.05	8	3	0.34	3	0	
Total cholesterol (mg/dl)	166 ± 32.2	152.8 ± 26.8	0.04	173 ± 31	154.8 ± 31.8	0.04	155.3 ± 9.1	148.4 ± 22.6	0.25
> 200	6	1	0.09	4	2	0.75	1	0	
HDL cholesterol (mg/dl)	51.7 ± 9.4	60.3 ± 9.4	0.003	50.1 ± 9.2	54.3 ± 9.5	0.09	58.6 ± 8.6	63.4 ± 10.4	0.10
< 40	2	0		2	0		0	0	
Triglycerides (mg/dl)	140.9 ± 40.4	118.7 ± 30.2	0.009	146.8 ± 35.9	131.6 ± 46.4	0.13	119.1 ± 35.6	118.7 ± 17.9	0.45
> 170	9	2	0.06	6	3	0.69	2	0	
Subjects with abnormal blood test values									
All	12	4	0.08	9	3	0.22	3	1	
Hb1aC > 5.7	2	2	0.79	2	0		1	1	
Impaired lipid metabolism*	1	1	0.85	1	0		1	0	
2 or more	9	1	0.01	6	3	0.69	1	0	
Drugs									
Antidiabetic agents	4	2	0.58	3	1	0.54	1	1	
Statins	0	1		0	0		1	0	
Antihypertensive drugs	2	1	0.70	1	1	0.74	1	0	
Caloric intake									
Adequate	28	24	0.41	17	11	0.92	15	9	0.62
Low	4	3	0.95	2	2	0.62	1	1	
High	4	1	0.26	3	1	0.54	2	0	

*Total cholesterol > 200 mg/dl and/or triglycerides > 170 mg/dl and/or HDL cholesterol < 40 mg/dl

lipid metabolism) and the release of bioactive peptides and hormones by the adipose tissue [6, 16].

However, to our knowledge, it is unknown whether in runners the first group of pathogenetic factors (overuse) or the latter (metabolic disorders) are more responsible for AT. Therefore, aim of the present study was to evaluate the factors pertinent to running modalities (frequency of sessions, kilometers run) and to the subject (demographic, anthropometric and biochemical), possibly associated with the onset of mAT in this specific sub-category of runners.

As expected, the study confirms the benefits of the running practice. In both groups, a significant weight loss and a reduction in BMI and in the percentage of overweight and obese persons were noticed. However, the more important finding is the observation that the subjects with mAT had a worse metabolic profile (significantly higher mean values

of Hb1aC, total cholesterol and triglycerides, and significantly lower HDL cholesterol) in comparison with runners without mAT. Accordingly, the percentage of pathologic values of metabolic parameters was significantly higher in the subjects with mAT. This condition which is strictly associated with the detrimental effects of metabolic disorders (cross-link within collagen fibers, cholesterol deposition and low-grade persistent inflammation) and overweight and/or obesity (release of bioactive peptides and hormones), frequently observed in the study group, on tendon structure, can explain the US pathological abnormalities (mild, moderate and severe) and neovessels inside the tendon.

Given that the running parameters (number of sessions and kilometers for week and cumulatively in the year) were equivalent in both groups, it may be supposed that metabolism disorders were the main responsible for mAT. The caloric intake was similar in the subjects of both groups; therefore, it is reasonable that the positive effects of running on metabolism in the subjects with tendinopathy were less significant.

This hypothesis raises several important questions. It is well known that exercise produces beneficial metabolic effects: increased insulin sensitivity and glucose uptake, release of fatty acids bound to albumin and of triglycerides stored in very low density lipoprotein, which are therefore utilized by skeletal muscles [17]. As result, a decrease in plasma levels of glucose and triglycerides, and at a lesser extent of total and LDL cholesterol, with a consensual increase in the levels of HDL cholesterol is observed. In addition, a substantial number of both longitudinal and cross-sectional studies have demonstrated positive effects on vascular endothelium, a reduction in the markers of inflammation and an increase in the density of capillaries in muscles [18]. In such a way, exercise represents a cornerstone in the primary prevention of a plethora of chronic conditions. All these processes are controlled by a complex interplay between neurohumoral regulators, intracellular signaling networks, posphorylation events, translocation of proteins within the cell, and protein–protein interactions. The efficiency of these pathways is strongly dependent by genetic factors [19].

In this framework, it must be noticed that significant variation exists in response to exercise in humans [20]. In controlled experimental situations, changes in aerobic exercise capacity, as measured by VO_2 max, can range from no gain in some individuals (non-responders) to 100% improvement in others (high responders) [21]. Moreover, non-responders to exercise training have a worse metabolic profile [22].

The results of the present study suggest that the runners with mAT were poor metabolizers. Therefore, the onset of the tendinopathy could be referred to the unfavorable metabolic milieu which amplifies the effects of overuse in tendons. Alternatively, we cannot exclude that genetic factors which predispose to AT can be involved [5]. Studies performed in South African and Australian cohorts concluded that genetic polymorphisms in IL-1β can contribute to the changes in inflammatory pathways and therefore may be important contributors to the risk of AT [23]. Polymorphisms in genes encoding caspases and nitric oxide synthases have also been investigated as these molecules had been shown to be involved in pathways accompanying tendon cell apoptosis, and their expression has been found to be elevated in tendinopathy [24]. Interestingly, these polymorphisms have been previously associated with gastrointestinal diseases [25], osteoporotic fractures [26] and atherosclerosis [27]. So, it would be interesting to evaluate whether some genes involved in the "metabolic resistance" to exercise can also predispose to AT.

Some limitations of the study must be acknowledged. Preliminarily, the retrospective nature of the study must be remarked. Data about the original motivation for running and running modalities were collected by means of a questionnaire (the subjects were not monitored digitally), and this introduces a recall bias. However, there are reasons to think that information collected was reliable. Indeed, the volunteers were very careful of their health conditions. Most of them wore a portable device and/or ran for the same amounts of kilometers in each session, and many performed blood evaluations of metabolic parameters [28]. On the other hand, self-reported diabetes, hypercholesterolemia and hypertension have been demonstrated reliable as confirmed by medical records (renal disorders was not reported) and have been used by the Nurses' Health Study and other major cohort studies [2, 29, 30]. As second important limitation is related to the effects of treatment modalities (drugs and their side effects, nutrition or dietary, alcoholism, smoking) in the study group; among them, the dietary habits were collected by means of a self-administered questionnaire, so that the real effect of the diet on metabolic parameters cannot be established.

Despite all this, the results of the study carry a relevant practical message. Given that a relative resistance of metabolic parameters to exercise is a possible risk factor for tendinopathy, such parameters should be monitored, and the physical activity should be tailored to each subject accordingly. Indeed, to increase the volumes of activity in the case of unsatisfactory diminution of body weight, blood lipids or Hb1aC would be deleterious.

As far as the directions of future research are considered, the best option would be to plan a study measuring at baseline, in subjects who start running, the metabolic parameters, and follow them for years, comparing afterwards those who undergo to AT to those free from the disease. It is evident that such a study should be time-consuming and hampered by several difficulties. At present, to enlarge the observation to genetic factors, mainly those regulating pathways which

could be common to obesity, metabolic disorders and tendinopathies, could be a more practicable road.

Compliance with ethical standards

Conflict of interest The authors disclose any conflicts of interest related to the research or the manuscript or to any previous presentation of the research, manuscript or abstract. They assure that authorship has been granted only to those individuals who have contributed substantially to the research or manuscript.

Ethical approval The procedure followed was in accordance with the Declaration of Helsinki, and the written informed consent was obtained from each patient.

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