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Elevated glycated haemoglobin affects Achilles tendon properties and walking capacity in healthy people without a diagnosis of diabetes

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The aim of this study was to test the hypothesis that individuals with an increase in HbA1c (i.e. above the regular but below the diabetic threshold) exhibit an impairment in the Achilles tendon structure and walking capacity, due to the adverse effect of the advanced glycation end-product. One hundred fifty-eight participants matched for gender, age, physical activity and BMI, were divided in two cohorts based on the HbA1c level: normal HbA1c (NGH; <39 mmol/molHb; *n* = 79) and altered HbA1c (AGH; >=39 mmol/molHb; *n* = 79). Each participant performed several walking trials to evaluate the kinematic parameters during walling at the self-selected speed and a quantitative MRI scan of the Achilles tendon (AT) to obtain its intrinsic characteristics (i.e. T2* relaxation time short and long component). The AT T2* relaxation time short component (a parameter related to the tendon collagen quality) was reduced in AGH compared to NGH. Furthermore, AGH exhibited a slower self-selected walking speed (NGH: 1.59 ± 0.18 m/s; AGH:1.54 ± 0.16 m/s) and a shorter stride length (NGH: 1.59 ± 0.13 m; AGH:1.55 ± 0.11 m). Our data suggest that a non-pathological increase in HbA1c is able to negatively affect AT collagen quality and walking capacity in healthy people. These results highlight the importance of glycemic control, even below the pathological threshold. Since diabetes could alter several biological pathways, further studies are necessary to determine which mechanisms and their timing, regarding the HbA1c rise, affect tendon composition and, consequently, walking capacity.

Keywords HbA1c, Achilles tendon, Gait, MRI, Tendon degeneration

Type 2 diabetes (T2D) could be considered one of the most common diseases in the elderly. According to the International Diabetes Federation (IDF, 2021), 536.6 million adults (10.8% of the world's male adult population and 10.2% of the female adult population) currently suffer from diabetes. By 2045, this number is projected to rise to 783.2 million, accounting for 12.2% of the global adult population, significantly impacting the healthcare system. Comprehending the structural and functional alteration associated with diabetes could aid in attenuating its adverse effects and, thereby, reducing healthcare costs.

In T2D, non-enzymatic glycation, induced by the advanced glycation end-products (AGEs), promotes cellular ageing and protein degeneration[1,2], which has been associated with a mechanical impairment of muscle-skeletal tissues[3]. For example, the non-enzymatic cross-linking of animal tendons due to an increased concentration of AGEs leads to changes in fibril morphology and a stiffening of this tissue[4–6]. On the other hand, elevated AGEs values in muscle induce atrophy through the proteolytic action of the ubiquitin-proteasome system and lead to muscle dysfunction[7,8]. Moreover, muscle-tendon dysfunction could also be associated with other diabetic-related alterations. Indeed, Burner et al.[9] showed that hyperglycemia reduces the proteoglycan production in porcine tendons, affecting collagen fibril formation and water content, which, in turn, determine the viscoelastic properties of tendons.

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In T2D patients, the morphological analysis of the Achilles tendon (AT) highlighted structural abnormalities that may be related to non-enzymatic glycation[10]. Furthermore, the elevated tendon cross-linking observed in people with T2D was associated with increased tendon stiffness during voluntary contraction[10] and walking[12]. Moreover, these mechanical disadvantages (e.g., impairment in the ankle range of motion) increased as a function of the disease duration[13] and with the diabetic complications (e.g., diabetic foot[14]. This abnormal tendon behaviour during locomotion in diabetic people may reduce ankle joint motion, which is correlated with step length and self-selected speed[15], reducing the locomotor capacity in this population. Thus, muscle-tendon dysfunction in diabetic patients has implications for everyday activities (e.g., walking).

Because of the gradual and asymptomatic onset of T2D, it may remain undiagnosed for years, during which muscle-tendon complications may progress unchecked. People with increased glycated haemoglobin and fasting plasma glucose than normal but lower than the diabetes threshold could be diagnosed with prediabetes[16], which represents a high-risk state for T2D for the affected people but they may prevent/delay T2D onset with physical activity and other lifestyle changes[17].

Recently,[18] demonstrated that prediabetic people have a three times higher risk of tendon injury of the lower limb than those in the healthy cohort. This evidence suggests that tendon structure deterioration begins at the glycated haemoglobin's rise, which induces collagen AGE-crosslinking[19,20]. To our knowledge, the prediabetic population was never characterized in terms of muscle-tendon structure and its effect on walking biomechanics.

Therefore, in this study, we used quantitative magnetic resonance techniques to evaluate AT structure and composition in people with a high risk of developing T2D (i.e. HbA1c exceeds the normal threshold but not the diabetic one) as well as the possible alteration of gait biomechanics. For these purposes, we compared two populations matched for age, gender, body mass index (BMI) and physical activity, except for the level of HbA1c. We hypothesized significant differences between populations in terms of quantitative magnetic resonance imaging (MRI) parameters and gait parameters. Specifically, we hypothesize a decrease in walking speed and stride length in people with altered levels of HbA1c. Moreover, we expect an increase in the AT T2* relaxation time (an MRI parameter related to the quality of the collagen[21], T2*rt) in this population.

Materials and methods

This study was part of a multidisciplinary research project, Healthy Ageing in the Industrial Environment (4HAIE), which investigated the long-term effect of air pollution on health and quality of life across the lifespan of a runner and physically inactive populations aged 18–65. The 4HAIE study adheres to the Declaration of Helsinki principles. The study protocol has been reviewed and approved by the Ethics Committee of the University of Ostrava (3/2018). The general methodology and protocol were presented by Cipryan et al.[22], Jandacka et al.[23] and Elavsky et al.[24]. The present study investigates the impact of AGEs accumulation on the AT structure and its subsequent effects on gait biomechanics.

Participants

Participants who experienced acute conditions that impeded physical activity within six weeks preceding the test, a diagnosis of diabetes, or were regular smokers were excluded from the study. Additional exclusion criteria for the 4HAIE study were the typical contraindications to MRI or Dual Energy X-ray Absorptiometry (DEXA) measurements (e.g. pregnancy, the presence of metal implants and foreign bodies). All participants gave their written informed consent for the experimental procedure. According to these criteria, 1314 Caucasian adults were recruited for the study.

Further exclusion criteria for this specific part of the project were: glycated haemoglobin levels higher than 46 mmol/mol (e.g., suggestive of a potential T2D[17];> 46); ongoing inflammation, clinical markers of AT pathology and previous ankle injury[25,26]. The presence of tendon inflammation or related problems was tested by means of a specific questionnaire[27]. Finally, only people older than 30 years have been included in this study.

Following these criteria, the participants were then divided according to the glycated haemoglobin cut-off for prediabetes, 39 mmol/molHb. Then, a 1:1 nearest neighbour matching was performed based on age, gender[14], activity status (i.e. runner/inactive) and BMI. If participants with an HbA1c alteration did not match with participants with a regular HbA1c for gender, age and activity status, they were excluded from the sample. Hence, the participants with an elevated HbA1c paired with a participant with a regular HbA1c and the matched participants with a regular HbA1c were considered in the altered HBA1c group (AGH, $n = 79$) and regular HbA1c group (RGH, $n = 79$), respectively, for further analysis. Figure S1 in Supplementary represents the flowchart of the study sample selection. For the sample selection, a custom Matlab script was used (MathWorks v. R2023b, Natick, MA, USA).

Experimental protocol

The participants visited the laboratories on one single occasion. First, biochemical data were collected in the morning hours (6:30 – 7:00 am). After that, magnetic resonance data of the right leg were acquired using a 1.5 T MRI system and the ACLS and retrospective running-related injury questionnaire were completed by each participant[26,28]. Finally, kinematic and kinetic data were collected during walking at the self-selected speed by the 4HAIE protocol[23].

Data collection

Blood sample

Fasting blood samples were collected from the antecubital vein in the early morning (6.30-7.00) to determine HbA1C, CRP and other blood parameters typically altered in metabolic syndrome patients (i.e. glucose, triglycerides, total cholesterol, HDL cholesterol and LDL cholesterol). CRP is an early inflammation biomarker

typically found in concentrations below 10 mg/L[30]. Thus, participants with values higher than 10 mg/L (i.e. possible inflammation) were not considered in this study.

Magnetic resonance imaging

Before the MRI protocol, subjects were required to sign a specifically informed consent form for this procedure, ensuring that they could safely undergo this evaluation without any associated risk. For the ankle imaging, subjects were positioned supine and feet-first in the MRI scanner bed (1.5 T; Siemens-Sempra, Erlanger, Germany). A 16-channel head coil with a custom device to fix the leg at 90° was used to scan the ankle joint with a focus on the AT. The protocol consisted of the morphological part using the axial "Turbo Spin Echo (TSE) T2-weighted", sagittal and coronal Spin Echo (SE) T1-weighted, axial and sagittal proton-density TSE fat-saturated weighted and a quantitative part using two identical gradient echo T2* sequences with a total of ten echo times. The sequence parameters were reported by Jandacka et al.[23]. During the 20 minutes of acquisition, participants avoided any unnecessary movements.

Questionnaires

In this study, questionnaires were mainly used to define the sample of the participants. Participants of the HAIE study who reported an ankle injury in the retrospective running-related injury questionnaire[26] and participants with a VIMAT score under 80 points were excluded[27]. VIMAT score (0-100, worst to best) consists of a questionnaire used by a radiologist to quantify the morphological evaluation of the AT[27]. Moreover, physical activity levels were assessed using the ACLS questionnaire[28].

Walking trials

Participants were instructed to walk at a self-selected speed overground. The lower body kinematics were recorded with a motion capture system (Oqus, Qualysis, Inc., Gothenburg, Sweden) at a sampling frequency of 240 Hz to assess gait parameters. Five reflective markers were placed on the heel and toe of the feet to determine stride length, stride cadence and stride width[30]. Participants were required to walk at their self-selected speed for about 12 m six times wearing neutral running shoes.

Data analysis

Achilles tendon evaluation

For the VIMAT score, thickness, continuity, signal intensity and associated pathologies were evaluated by a radiologist from the morphological part of the MRI protocol.

The T2*rt short and long components of the whole AT and its portion (i.e. insertion, middle portion, muscle-tendon junction) were determined from sagittal T2-weighed images. The short and long components reflect increased content of bound or unbound "free" water molecules, respectively. Furthermore, a higher value of T2*rt short component was related to superior collagen quality[21].The T2*rt short and long components of the whole AT and its portion (i.e. insertion, middle portion, muscle-tendon junction) were determined from sagittal T2-weighed images. The regions of interest (ROI) (i.e. portions of the AT) were manually defined with a custom Matlab script (MathWorks v. R2020a). The T2*rt was calculated at whole tendon levels and for its portion. It was estimated from the bi-exponential fitting of the mean intensity of the ROI in the correspondent echo time. The Eq. (1) (i.e. bi-exponential fitting) allows to determine the short and long components of the T2*rt:

$$SI = A_O{}^{-TE/A_1} + A_2{}^{-TE/A_3} + A_4 \quad (1)$$

where SI is the signal intensity, TE the echo time, A_0 and A_2 are the component ratios, A_1 and A_3 represents the short and long T2*rt components, respectively, and A_4 is the offset (primarily noise).

Walking trials

Kinematic data were analysed using QTM (Track Manager, Qualysys, Sweden, Gothenburg) and Visual3D software (C-Motion, Germantown, Kentucky, KY, USA). Stride events, such as heel strike and toe-off, were detected automatically with an algorithm based on Stanhope et al.[31]. Based on these events, it was possible to determine the stride length as the distance of the heel marker between two consecutive ipsilateral heel strikes, stride cadence as stride per minute, stride width as the mediolateral distance of the heel marker between the ipsilateral and contralateral heel strikes and the walking speed as the ratio between the stride length and the stride time. The average stride length, stride cadence, stride width, and speed of the six trials for each subject were considered for further analysis.

Statistical analysis

Shapiro-Wilks test was used to check data normality. Independent t-tests were used to assess differences in the anthropometric characteristics and biochemical profile. A Chi-test was used to determine differences in the gender proportion between groups. Moreover, an independent t-test was applied to determine the differences between the MRI and the walking parameters investigated. Furthermore, Cohen's d effect size was evaluated and interpreted according to the cut-off proposed by Cohen[33]: $d < 0.2$, trivial effect; $0.2 < d < 0.5$, small effect; $0.5 < d < 0.8$, moderate effect; $d > 0.8$ large effect. In case of non-normality of the data, Mann Whitney U and rank biserial correlation were used. The level of significance was set at $P < 0.05$. Statistical analyses were performed using Jamovi (v2.4.11).

	NGH ($n=79$)	AGH ($n=79$)	p-value
Gender (M/F)	43/36	43/36	1
Age (years)	46.99 ± 7.85	46.99 ± 7.85	1.000
Physical activity (METs)	28.35 ± 25.96	29.66 ± 23.96	0.569
Mass (kg)	80.73 ± 12.89	82.17 ± 14.80	0.516
Height (m)	1.77 ± 0.10	1.76 ± 0.08	0.342
BMI (kg m^{-2})	25.76 ± 2.95	26.56 ± 4.28	0.244
HbA1c (mmol $molHB^{-1}$)	34.34 ± 2.53	40.28 ± 1.62	< 0.001
Glucose (mmol L^{-1})	4.87 ± 0.45	5.04 ± 0.48	0.028
Triglycerides (mmol L^{-1})	1.13 ± 0.47	1.30 ± 0.70	0.062
Total cholesterol (mmol L^{-1})	5.08 ± 0.95	5.11 ± 0.88	0.870
HDL cholesterol (mmol L^{-1})	1.61 ± 0.47	1.52 ± 0.44	0.193
LDL cholesterol (mmol L^{-1})	3.25 ± 0.98	3.29 ± 0.84	0.738
CRP (mg L^{-1})	1.63 ± 1.20	1.83 ± 1.34	0.457

Table 1. Participants characteristics (data are mean ± SD). BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoproteins; LDL, low-density lipoproteins; CRP, C-reactive protein.

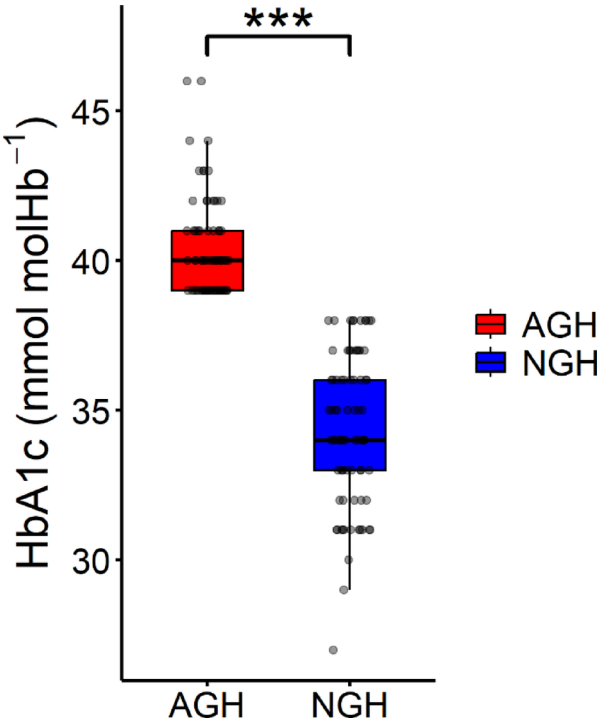

Fig. 1. HbA1c values in the investigated cohorts. Data in blue refers to NGH, whereas data in red refers to AGH. Dots represent individual data. Box plots with 1st and 3rd quartile, whiskers (1st quartile − 1.5 * interquartile range; 3rd quartile + 1.5 * interquartile range) and median as the horizontal line are represented as well. * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Results

The participants' characteristics are reported in Table 1. No significant differences were observed between groups in age, gender, physical activity, body mass, body height, BMI, or any of the investigated blood parameters, except for the HbA1c (Fig. 1) and the glucose levels that were higher in the AGH (HbA1c: $p<0.001$, ES = 2.795; glucose: $p=0.003$, ES = 0.356).

In Fig. 2, T2*rt short and long component data are reported. Lower T2*rt short component values in the mid-portion ($p=0.006$, ES = 0.278) and whole AT ($p=0.002$, ES = 0.215) were observed for AGH, compared to NGH. No significant differences between groups were observed for the T2*rt long component in all the investigated AT portions (insertion, $p=0.411$, ES = 0.086; middle portion, $p=0.427$, ES = 0.081; muscle-tendon junction, $p=0.247$, ES = 0.113; whole, $p=0.081$, ES = 0.161).

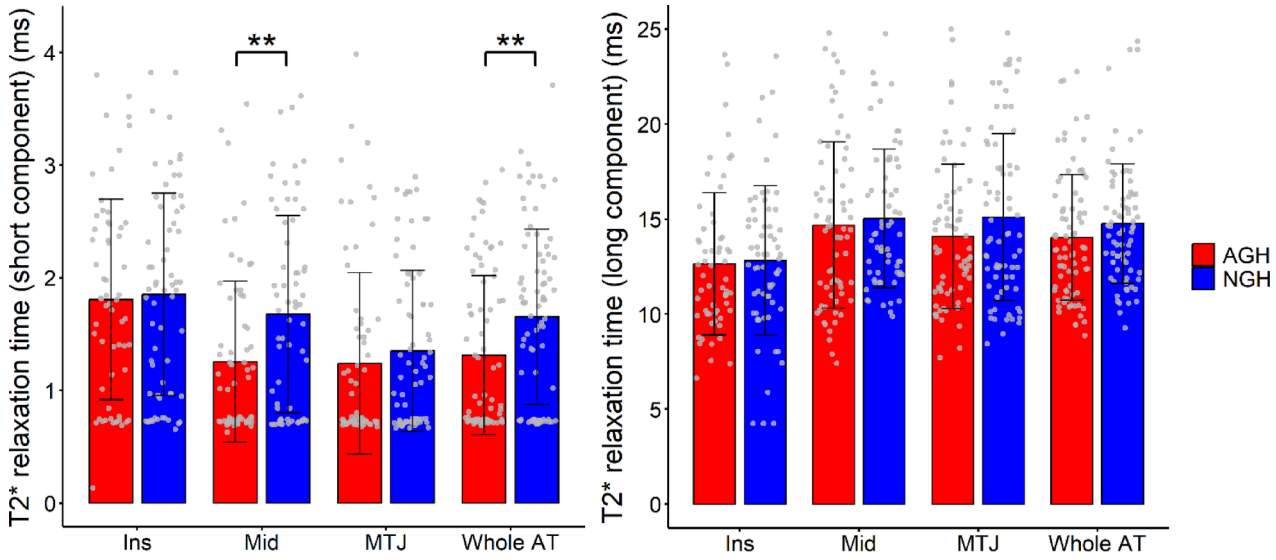

Fig. 2. T2* short (left panel) and long (right panel) components in the investigated cohorts. Data in blue refers to NGH, whereas data in red refers to AGH. Dots represent individual data. Mean value and standard deviation are reported as well. Abbreviations: Ins, insertion; Mid, middle portion; MTJ, muscle-tendon junction. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

	NGH	AGH	*p*-value	Cohen's d
Self-selected speed (m s^{-1})	1.59 ± 0.18	1.54 ± 0.16	0.045	0.328
Stride length (m)	1.59 ± 0.13	1.55 ± 0.11	0.044	0.189
Stride cadence (stride min^{-1})	60.12 ± 4.28	59.61 ± 3.89	0.448	0.124
Stride width (m)	0.13 ± 0.02	0.13 ± 0.03	0.227	0.197

Table 2. Walking parameters investigated (mean ± SD) in the two groups. P-values and Cohen's *d* are indicated as well.

In Table 2, the gait parameters are reported. The self-selected walking speed ($p = 0.045$, ES = 0.328) and the stride length ($p = 0.044$, ES = 0.189) were lower in AGH compared to NGH. No significant differences were observed in stride cadence ($p = 0.448$, ES = 0.124) and stride width ($p = 0.227$, ES = 0.197).

Discussion

This study used quantitative MRI techniques to compare AT material properties between people with and without altered levels of HbA1c. Furthermore, we tested the hypotheses that higher values of HbA1c, even without the diagnosis of type 2 diabetes, could affect not only the AT characteristics but also the walking capacity of these participants. To do that, we recruited two cohorts, none of them with the presence of diabetes or metabolic syndrome (i.e. obesity, elevated blood pressure, triglycerides and glucose, and low high-density lipoprotein cholesterol)[33]. Moreover, our cohorts were matched by age, gender and physical activity factors to minimize potential confounding variables[14].

In agreement with our first hypothesis, we observed significant differences between populations in terms of T2*rt short components (middle portion and whole AT) and gait parameters (walking speed, stride length and stride frequency). In particular, people with altered levels of HbA1c exhibited lower T2*rt values, lower walking speed and shorter stride length compared to people with normal values of HbA1c, suggesting an impairment in collagen quality and walking capacity in people with AGH.

Our data suggest that the AGH group's midportion and the whole AT had less bounded water and collagen fibres organisation compared to NGH. Indeed, T2*rt is the decay constant in the signal intensity of soft tissue, such as cartilage and tendons, as a function of the echo time[34]. Using a bi-exponential fitting of this curve, it is possible to determine the short and long components of T2*rt, which are related to the bound and unbound water molecules, respectively[35]. While the first has clinical relevance in determining the organization of collagen fibres, the latter detects acute changes at the tissue level[36].

The small change of the short component of T2*rt observed in healthy people with an elevated HbA1c could be explained by an increased AGEs content and, consequently, a reduction of the synthesis of proteoglycans in a hyperglycemic environment[37,38]. Indeed, the alteration of AGEs and proteoglycans content has an adverse effect on collagen turnover, affecting the fibrillogenesis process[39] and fibroblast apoptosis[40], which underpins the structural organization of the tendon tissue. Moreover, the AGEs-mediated lower electron transfer efficiency

and the increased reactive oxygen species expression contribute to damage to the tendon structure through an inflammation status[40,41]. Finally, the disruption of the collagen network facilitates the release of the trapped water molecules, reducing the T2*rt short component[42]. However, no differences were appreciated in terms of T2*rt long component, possibly due to the absence of tendon short-term adaptations related to the increase of HbA1c. Indeed, HbA1c reflects glucose metabolism impairment over the past two/three months that leads to an AGE accumulation over time and causes tendon degeneration. The difference in collagen quality was observed in the mid-portion of the tendon, and it could represent the consequence of the initial inflammatory process that could lead to tendon rupture in the future. Noteworthy, AT rupture typically occurs 3–6 cm above the calcaneal insertion[43], along with an impairment of fibrils of the core of the tendon[44]. Significant differences between populations in the T2*rt short component were also observed at the whole tendon level, due to the calculation of this parameter. Indeed, the signal intensity (on which the T2*rt is based) for the whole AT is determined as the sum of those obtained in each AT portion. Thus, differences in the mid-portion of the AT lead to differences in the whole AT.

In people with increased levels of HbA1c, a small but significant reduction in stride length (about 0.04 m) and self-selected speed (about 0.04 m/s) was observed. Taking into account the degree of the pathology and the age-related walking impairment[45], our results are in agreement with the previous literature[12,15,46]. In diabetic cohorts compared to age-matched healthy participants, they observed a reduction in self-selected speed (about 0.10 m/s in diabetic patients and 0.15 m/s in neuropathic diabetic patients) and a shorter stride length (about 0.10 m in neuropathic diabetic patients), whereas no differences were observed in stride cadence as in Martinelli et al.[15]. Therefore, our results suggest an impairment in walking capacity even without a diagnosis of diabetes.

Further considerations and limitations

This study has a cross-sectional design able to identify differences between populations but not the cause-effect relationship. Indeed, the changes in AT T2*rt observed in this present study suggest a significant alteration of the collagen structures[21,36] in people with altered values of HbA1c, which in turn could (at least) partially affect their walking capacity. An impairment in collagen quality could affect the AT Young's Modulus[21], increasing tendon hysteresis during walking Indeed, the changes in AT T2*rt observed in this present study suggest a significant alteration of the collagen structures[21,36] in people with altered values of HbA1c, which in turn could (at least) partially affect their walking capacity. An impairment in collagen quality could affect the AT Young's Modulus[21], increasing tendon hysteresis during walking[12] and reducing the AT stretch-shortening capacity[13]. Therefore, it is possible to assume that the hyperglycemic environment that leads to an HbA1c increase could have a negative effect on AT tissue quality through the AGE-related crosslinking and cell inflammation, but the cause-effect relationships should be verified in future studies.

Even if the precision of the fitting curves suggested that a bicomponent analysis was a valid and reliable tool to investigate T2*rt, we adopted an MRI scan with a magnetic field of only 1.5 Tesla and, therefore, we weren't able to use UTE imaging. Further studies with higher magnetic intensity (e.g., 3 Tesla) could provide further insights into the reported correlations.

Conclusions

This study suggests that an increase in HbA1c, even without the presence of diabetes, could represent a potential risk marker of an impaired walking pattern and tendon tissue. Our findings highlight the importance of glycemic control: a slight increase in HbA1c could represent the pro-inflammation process that leads to an impairment in walking capacity and an alteration of tendon quality in the most vulnerable AT portion.

Data availability

Data is provided within the manuscript or supplementary information files.

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Author contributions

JU, DJ obtained funding for this project. RM, AM conceptualized and designed the study. JU, LC, and JS were involved in data collection and analysis. RM, AM conducted sample selection and statistical analysis. RM wrote the first draft of the manuscript which was critically revised by all authors.

Declarations

Competing interests
The authors declare no competing interests.

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