

# Persisting side-to-side differences in bone mineral content, but not in muscle strength and tendon stiffness after anterior cruciate ligament reconstruction

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## Summary

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Tendon stiffness may be involved in limiting peak musculoskeletal forces and thus may constitute an upper limit for bone strength. The patellar tendon bone (PTB) graft, which is harvested from the patellar tendon during surgical reconstruction of the anterior cruciate ligament (ACL), is an ideal scenario to test this hypothesis. Eleven participants were recruited who had undergone surgical reconstruction of the ACL with a PTB graft 1–10 years prior to study inclusion. As previously reported, there was no side-to-side difference in thigh muscle cross-sectional area, in maximum voluntary knee extension torque, or in patellar tendon stiffness, suggesting full recovery of musculature and tendon. However, in the present study bone mineral content (BMC), assessed by peripheral quantitative computed tomography, was lower on the operated side than on the control side in four regions studied ( $P = 0.0019$ ). Differences were less pronounced in the two sites directly affected by the operation (patella and tibia epiphysis) when compared to the more remote sites. Moreover, significant side-to-side differences were found in BMC in the trabecular compartment in the femoral and tibial epiphysis ( $P = 0.004$  and  $P = 0.047$ , respectively) with reductions on the operated side, but increased in the patella ( $P = 0.00016$ ). Cortical BMC, by contrast, was lower on the operated side at all sites except the tibia epiphysis ( $P = 0.09$ ). These findings suggest that impaired recovery of BMC following ACL reconstruction is not because of lack of recovery of knee extensor strength or patellar tendon stiffness. The responsible mechanisms still remain to be determined.

## Introduction

Tears of the ACL are common. In patients with an ACL tear who develop recurrent giving way, surgical reconstruction of the ACL is undertaken. PTB graft is commonly used for this purpose (Kapoor et al., 2004; Spindler et al., 2004; Busam et al., 2008).

Bone loss has been reported both following ACL injury and after surgical reconstruction (Andersson & Nilsson, 1979; Kannus et al., 1992; Sievanen et al., 1996; Leppala et al., 1999). This bone loss seems to be greater in patients who underwent reconstruction than in those who were managed conservatively (Leppala et al., 1999). In patients who underwent surgery, bone losses were more pronounced at the skeletal sites directly affected by surgery than in regions that were remote to it

(Leppala et al., 1999). Recovery of these losses is only moderate to poor (Kannus et al., 1992).

Bones adapt to mechanical stimuli, and strains within bone are crucially involved in this (Rubin & Lanyon, 1985, 1987). According to the mechanostat theory, peak strains constitute the controlled variable in a negative feedback control system (Frost, 1987). The largest forces that the long bones experience arise from muscle action rather than from mere gravitational forces (Özkaya & Nordin, 1998; Rittweger, 2007). Hence, differences in musculature constitute a logical explanation for inter-individual variation in bone strength (Schiessl et al., 1998; Rittweger et al., 2000, 2006).

In line with this view, resistive exercise can prevent bed rest-induced bone losses when muscle strength is maintained

(Rittweger et al., 2010) or even increased (Shackelford et al., 2004), but not when it is insufficient to prevent muscular atrophy (Alkner & Tesch, 2004; Watanabe et al., 2004; Rittweger et al., 2005a). Thus, muscular exercise is able to prevent immobilization-induced bone losses, which can amount up to 50% in patients after spinal cord injury (Eser et al., 2004). On the other hand, enhancement of bone strength by muscular exercise in healthy adults is very hard to achieve and usually does not exceed 1–2% (Kohrt et al., 2004; Martyn-St James & Carroll, 2006). Conversely, recent observations from the follow-up of bone losses incurred during bed rest (Rittweger & Felsenberg, 2009) and space flight (Lang et al., 2006; Sibonga et al., 2007) suggest that bone gains are astoundingly rapid in the early recovery period, so that the rate of accrual is comparable to the pubertal growth spurt (Rittweger & Felsenberg, 2009). However, the salient ability to accrue bone mass comes to a halt once the status quo ante is achieved.

Therefore, it has been postulated that habitual generation of muscular forces is limited by a yet unknown mechanism, thus constituting an effective peak bone strength (Rittweger, 2008). More specifically, it has been proposed that tendon strain could be limited by the motor control system to constitute such a mechanism (Rittweger et al., 2005b; Rittweger, 2008). The clinical model of PTB harvest for ACL reconstruction can offer an opportunity to scrutinize that hypothesis, as removal of the middle one-third of the patellar tendon in this procedure should lead to a reduced patellar tendon stiffness. According to our hypothesis, this should lower the peak habitual forces and thus cause persisting loss of bone tissue on the operated side (Rittweger et al., 2005b). Indeed, a reduction in isometric knee extensor strength by 8% to 10% has been reported on the operated side 12 months after ACL reconstruction (Rutherford et al., 1998; Leppala et al., 1999). Moreover, functional deficits because of ACL injury have been reported to be correlated with a bone deficit (Kannus et al., 1992), altogether underlining the importance of an optimal surgical and physiotherapeutic approach. However, as recently reported, patellar tendon stiffness is restored after ACL reconstruction with the PTB graft (Reeves et al., 2009), and we could not demonstrate any side-to-side difference in knee extensor volume or strength in that cohort (Reeves et al., 2009). Accordingly, we hypothesized that bone mass would also be recovered on the operated side in that same cohort.

## Materials and methods

### Study design

A retrospective, cross-sectional study was undertaken to compare side-to-side differences in the operated (OP) and the non-operated (Ctrl) leg with regard to bone and muscle strength and patellar tendon stiffness. Male participants were recruited by poster advertisements and through the local media. Participants were eligible when they had undergone PTB surgery more than 12 months prior to the study, unless they reported complica-

tions in relation to the operation or unsatisfying clinical outcome. An a-priori sample size estimation was carried out, assuming a standard deviation (SD) for the side-to-side difference in bone mineral content (BMC) of 3% [based on baseline data from two previous studies (Rittweger et al., 2005a, 2010)], and with  $\alpha = 0.05$  and  $1 - \beta = 0.8$ . The result indicated that eight participants would suffice to detect a side-to-side difference of 3%. The study was approved by the local ethics committee, and all participants gave their written informed consent prior to inclusion.

### History and clinical assessment

All subjects had undergone ACL surgery using the PTB graft between 1 and 10 years prior to testing. The contralateral leg was free from injury and had not previously undergone any form of surgery. The function of the operated knee was assessed using the Cincinnati questionnaire (Li et al., 1996). Anterior knee laxity was defined by the ventral displacement elicited by a brisk pull of the shank by one of the investigators (N.D.R.). It was assessed for both OP and control knees using a rolimeter (Aircast, Austin, TX, USA) (Balasch et al., 1999; Ganko et al., 2000).

### Patellar tendon stiffness

Patellar tendon stiffness was assessed *in vivo* during an isometric contraction using a combination of ultrasound imaging and dynamometry. The tendon's stiffness was quantified from the gradient of its force-elongation curve. Maximum isometric knee extension joint torque was assessed at a 90° knee angle on the dynamometer. Whilst the point of force application on the dynamometer's lever arm was applied at a similar distance between the two legs (for the purpose of lower limb comfort), joint torque was directly measured by the dynamometer and therefore any variations in this distance (lever arm) would not alter the measured torque. Anatomical cross-sectional area (CSA) of the quadriceps muscles was measured from axial plane magnetic resonance images. Further details of these procedures are described elsewhere (Reeves et al., 2009).

### Bone scans

Bone scans of the knee were obtained by peripheral quantitative computed tomography (pQCT) (Rittweger et al., 2000) using an XCT2000 (Stratec Medizintechnik, Pforzheim, Germany). In brief, the tibia length was assessed as the difference between the most prominent point of the medial malleolus and the medial knee joint cleft. The femur length was assessed as the distance between the lateral knee joint cleft and the tip of the greater trochanter. Next, a pQCT scout view was obtained in the sagittal plane, ranging from approximately 1 cm above the patella to approximately 1 cm distal of the insertion of the patellar tendon into the tibia. From this scout view, a reference line was set to the distal femur surface and to the distal tibia plateau, and the

length of the patella was also measured from the scout view. The control leg (non-operated side) was always measured first, and the patella length of the control side was used for the operated side, to account for a potentially shorter patella owing to the surgical intervention. Four scans were then obtained, namely at the proximal tibia epiphysis and metaphysis at 96% and at 86%, respectively, of the tibia length from its distal end, at the femur epiphysis at 4% of the femur length from its distal end and at 70% of the patella length from its distal end (Fig. 1a). The choice of the measurement sites in the tibia was such that the 86% position was distal, and the 96% position was just proximal of the patellar tendon insertion. The choice of the 70% position for the patella scan was based on prior pilot testing, which had yielded greatest BMC at that site.

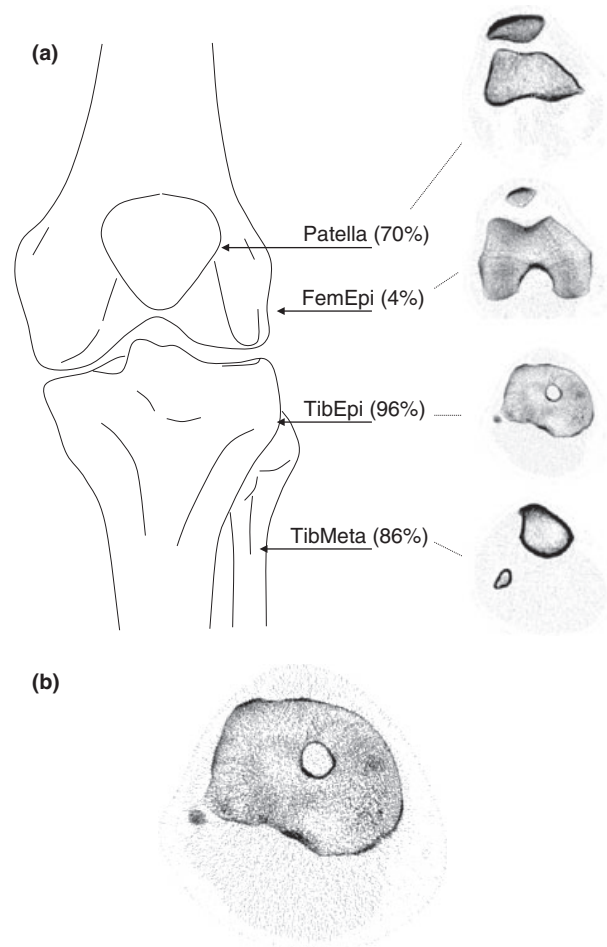
### Image data processing

pQCT images were further analysed with the integrated XCT software in its version 5.50D (Stratec Medizintechnik, Pforzheim, Germany). Thresholds for the detection of bone contours were set to  $650 \text{ mg cm}^{-3}$  for the tibia metaphysis and to  $180 \text{ mg cm}^{-3}$  for the tibia and femur epiphysis and for the patella (Wilks et al., 2009). For the latter 3 regions, care was taken to exclude the soft tissue from the regions of interest used for analysis.

The nomenclature chosen for acronyms follows the suggestions for reporting high-resolution CT results (<http://nomenclature.bb.asbmr.org>), given that there is currently no standardized nomenclature for pQCT results. For all regions, we extracted total volumetric bone mineral content (vBMC.tot) and total bone area (Ar.Bo) by an automated 'loop' analysis. Moreover, we assessed the volumetric bone mineral content attributable to compact bone (vBMC.Ct). The latter was identified by the variable CRT\_CNT from the loop database, with the contour mode set to 1 and a detection threshold of  $650 \text{ mg cm}^{-3}$ . For each sectional image, the volumetric bone mineral content attributable to trabecular bone (vBMC.tb) was then computed as  $\text{vBMC.tb} = \text{vBMC.tot} - \text{vBMC.Ct}$ , as previously described (Rittweger et al., 2009).

### Statistical analyses

For greater stability of statistical models, analyses were performed on the data expressing the percentage difference between the OP and Ctrl sides (percentage difference =  $100\% [(OP/Ctrl) - 1]$ ). For each variable (vBMC.tot, vBMC.Ct, vBMC.tb and Ar.Bo), linear mixed-effects models (Pinheiro & Bates, 2000) were used to fit a model with a fixed effect of 'measurement region' (femur epiphysis, patella, tibia epiphysis, tibia metaphysis). Random effects for each subject were permitted. Where necessary, allowances were made for the heterogeneity of variance owing to measurement region. Subsequent analysis of variance (ANOVA) examined the significance of each of the factor and the intercept term. An  $\alpha$  of 0.05 was taken for statistical significance. Where suggested by



**Figure 1** (a) Overview of the four different measurement sites, namely the patella, the distal femur epiphysis (FemEpi), the proximal tibia epiphysis (TibEpi) and tibia metaphysis (TibMeta). The values in brackets are the measurement positions relative to a particular bone's length, starting from the distal end of the bone. (b) Close-up of the proximal tibia epiphysis in A. The central canal through which the tendon graft is conveyed can be appreciated. Please note the compact bone tissue surrounding the canal. All such images have been included into the analysis.

ANOVA, *a priori* contrasts were then performed to compare between body regions for each variable. To further investigate any significant side-to-side differences, we tested for differences in those regions that were directly affected by the operation (*local*: tibia epiphysis and patella) versus the regions *remote* to the operation (femur epiphysis and tibia metaphysis). Data are presented as mean and SD, unless indicated otherwise. All analyses were performed in the 'R' statistical environment (version 2.9.2, <http://www.r-project.org>).

### Results

Eleven participants were involved in this study. Their anthropometric characteristics are given in Table 1. Anterior knee joint laxity was larger on the OP side than on the Ctrl side [ $7.1$  (SD  $1.9$ ) mm versus  $4.7$  (SD  $1.1$ ) mm,  $P = 0.0028$ ]. No significant

**Table 1** Anthropometric characteristics of the study participants, as well as time since the operation and the Cincinnati score.

n = 11	Mean (SD)	Range
Age (years)	36.1 (13.9)	20–61
Height (cm)	178.5 (6.6)	166–187
Mass (kg)	78.3 (11.6)	56–96
Time since operation (months)	66.6 (36.7)	12–117
Cincinnati score	83.5 (11.4)	58–96

**Table 2** Side-to-side comparison of volumetric bone mineral content (vBMC) of the entire bone (vBMC.tot), of its trabecular (vBMC.tb) and compact (vBMC.Ct) portions, as well as total bone area (Ar.Bo) on the operated (OP) and non-operated (Ctrl) sides in the four different regions investigated in this study. Values are mean (SD). The variable case numbers arise from scans that had to be rejected because of the presence of metal screws.

Leg	Femur epiphysis n = 9	Patella n = 6	Tibia epiphysis n = 5	Tibia metaphysis n = 8
vBMC.tot (mg mm <sup>-1</sup> )				
OP	1187 (153)	358 (61)	858 (127)	548 (65)
Ctrl	1250 (153)	370 (74)	877 (135)	579 (69)
Ar.Bo (mm <sup>2</sup> )				
OP	4251 (449)	715 (119)	3661 (211)	1214 (92)
Ctrl	4318 (327)	666 (108)	3512 (298)	1182 (78)
vBMC.Ct (mg mm <sup>-1</sup> )				
OP	104 (47)	150 (39)	56 (25)	377 (31)
Ctrl	105 (35)	180 (51)	34 (10)	403 (48)
vBMC.tb (mg mm <sup>-1</sup> )				
OP	1083 (123)	208 (32)	802 (125)	172 (40)
Ctrl	1145 (131)	190 (26)	843 (128)	176 (36)

correlation was found between anterior knee joint laxity and age or time since operation. Likewise, there was no correlation between the side-to-side difference in laxity and age or time since OP.

Patellar tendon stiffness was  $4386 \pm 1514$  N mm<sup>-1</sup> on the OP and  $4405 \pm 1282$  N mm<sup>-1</sup> on the Ctrl side ( $P > 0.05$ ). Maximum isometric knee extensor torque was  $228 \pm 70$  Nm

on the OP and  $229 \pm 66$  Nm on the CTRL side ( $P > 0.05$ ). Quadriceps muscle CSA was  $44 \pm 9$  cm<sup>3</sup> on the OP and  $46 \pm 9$  cm<sup>3</sup> on the CTRL side ( $P > 0.05$ ).

As expected, images from the proximal tibia epiphysis depicted a central canal where the patellar tendon graft was hosted (see Fig. 1b). These canals were delimited by a layer of compact bone (see Fig. 1b). The bone tissue from this layer has been included in the measurement of vBMC.Ct at this skeletal site.

Table 2 gives the absolute values for each of the measurement variables for each region. Analyses performed on the percentage differences (Table 3) showed significant side-to-side differences in vBMC.tot ( $F = 14.6$ ,  $P = 0.0019$ ), were consistent across all measurement regions ( $F = 0.9$ ,  $P = 0.47$ ), and on average the operated side had  $-4.2\%$  (1.1) ( $P = 0.00089$ ; mean (SEM)) lower vBMC.tot than the non-operated side. Further analysis showed that the side-to-side differences in vBMC.tot were greater in the remote regions (tibia metaphysis, femur epiphysis;  $P = 0.0013$ ), amounting to  $-5.4\%$  (1.3) compared to  $-1.9\%$  (1.4) closer to the operated area.

vBMC.Ct was lower on the operated side in the patella ( $P = 0.0036$ ; Table 3) and tibial metaphysis ( $P = 0.0074$ ), but increased non-significantly on the operated side at the tibial epiphysis ( $P = 0.09$ ). vBMC.tb was lower on the operated side in the femoral epiphysis ( $P = 0.004$ ) and tibial epiphysis ( $P = 0.047$ ), but comparable between sides ( $P = 0.7$ ) at the tibial metaphysis, and it was increased on the operated side at the patella ( $P = 0.00016$ ). Ar.Bo was significantly higher on the operated side at the patella ( $P = 0.017$ ; Table 3) and tibial epiphysis ( $P = 0.037$ ), but otherwise non-significantly different to the non-operated side at the tibial metaphysis and femoral epiphysis.

## Discussion

The total vBMC on the operated leg was reduced to a similar extent across all measurement regions. However, there were no side-to-side differences in knee extensor muscle size and force, or in patellar tendon stiffness in this cohort 1–10 years after PTB graft surgery (Reeves et al., 2009), suggesting complete recovery

**Table 3** Data are mean (SEM) percentage difference between operated and non-operated sides. Negative values indicate the operated side has a lower bone content/area than the non-operated side (see also Table 2).

Variable	Femoral epiphysis n = 9	Patella n = 6	Tibial epiphysis n = 5	Tibial metaphysis n = 8	ANOVA	
					P-value for differences between regions	Pooled across regions
vBMC.tot	$-5.4$ (1.7)%*	$-2.8$ (1.8)%	$-2.0$ (2.3)%	$-5.3$ (1.7)%*	0.469	$-4.2$ (1.1)%**
Ar.Bo	$-1.7$ (1.7)%	$7.4$ (2.7)%***	$4.5$ (1.9)%***	$2.7$ (1.5)%	0.0446	$2.7$ (1.0)%***
vBMC.Ct	$-1.3$ (8.9)%	$-18.2$ (5.2)%*	$72.6$ (40.7)%	$-6.3$ (2.0)%*	0.0074	$-6.6$ (2.0)%*
vBMC.tb	$-5.3$ (1.6)%*	$9.1$ (1.8)%**	$-4.8$ (2.2)%***	$-2.0$ (5.8)%	0.0002	$-4.4$ (1.2)%*

\* $P < 0.01$ ; \*\* $P < 0.001$ ; \*\*\* $P < 0.05$  indicate significance of percentage value compared to zero.

ANOVA P-value indicates whether the variation across regions was significant.

The final column indicates the percentage difference when pooled across all measurement regions.

of the regional muscles and tendon properties. There was no relationship ( $R^2 = 0.16$ ) between the time since operation and the percentage tendon stiffness difference between control and operated sides, indicating that the majority of adaptations occurred within the first 12 months postoperation (Reeves et al., 2009). Indeed, this hypothesis is consistent with the observations of tendon adaptations to chronic disuse (Maganaris et al., 2006). Therefore, patellar tendon stiffness does not seem to be responsible for the reduced bone strength on the operated side.

Thus, the question arises as to which mechanisms could be responsible for the BMC reduction in the operated leg. Theoretically, it is possible that the structural design has been enhanced by some unknown mechanism by the surgical intervention, and that the existing bone mineral could have become arranged in a more efficient way. This notion is actually supported by our findings in the proximal tibia epiphysis, where we found reduction in total and trabecular BMC, but an increase in compact BMC on the operated side. It should be remembered here that the apparent stiffness and strength of trabecular bone networks increase with apparent bone mineral density in a non-linear way such that the bone structure becomes increasingly strong and stiff with increasing density of the trabecular network (Ebbesen et al., 1997). More specifically, the relation between ultimate stress ( $\sigma$ ) and apparent density ( $\rho$ ) is well explained by

$$\sigma = \rho^a$$

which is a power relationship in which exponent  $a$  is somewhere between 2 and 3, depending on the anatomical location of the tissue (Ebbesen et al., 1997). Accordingly, and in relation to BMC, we can regard compact bone tissue as a more material efficient way to build bones than trabecular bone. Therefore, the accumulation of compact bone tissue around the central bore (see Fig. 1b) would be expected to contribute more to whole-bone strength and stiffness than an equal amount of trabecular bone would, and it is possible that the whole-bone strength is comparable on the OP and on the Ctrl side in the proximal tibia epiphysis. However, it would be hard to see how this could apply to the other regions examined in this study. Admittedly, trabecular BMC was even increased on the operated side in the patella, but total BMC and compact BMC were both decreased. Apparently, cortical bone has been transformed into trabecular bone here. Accordingly, as explained above, we have to assume that whole-bone strength is reduced on the operated side of the patella, and this is also undoubtedly true for the femur epiphysis and for the tibia metaphysis. Of note, the latter two sites are remote to the surgical intervention, and losses were more pronounced in these regions than in those directly affected by the operation. Taken together, these findings suggest that surgery in itself is not the reason for the permanent bone loss after ACL reconstruction, an interpretation that could emerge from DXA-based studies (Leppala et al., 1999). On the other hand, it is also possible that the ACL graft induces novel, non-physiological strains as it passes through the tibia, and that this

engenders bone formation to form the 'surgical' canal. We tend to favour this interpretation, which obeys Occam's razor (i.e. that entities must not be multiplied beyond necessity), as the interpretation of bone strength on the operated side being equally reduced across all four sites measured, plus the assumption of novel local strains in the proximal tibia engendering local bone formation is a more economic assumption. Whilst we consider this to be the most likely explanation, other factors, such as muscle power, or even subtle alterations in habitual gait patterns after surgery, may be associated with the side-to-side bone differences. Future work should also consider such factors as well.

The increased total bone area on the operated side in the patella and in the proximal tibia epiphysis are peculiar findings, which may arise from a combined precision and sample size problem, in particular for the patella which is a challenging target for the determination of cross-section. Some limitations of this study have to be discussed. First, the entire argument in the present investigation has been based upon side-to-side differences at one point in time. The underlying assumption is that ACL injury and surgery would have a direct effect upon the affected limb. Conversely, it is also possible, and to a certain extent perhaps even likely, that there is an effect on the contralateral limb, too. Such generalized effects cannot be explored by the present approach. However, this can only lead to an underestimation of the incomplete recovery observed, and it would therefore introduce a conservative error in relation to our main conclusion.

Secondly, one could speculate that the period of observation was not long enough, and that full recovery of bone losses could occur at a later stage. It should be noticed in response to this objection that bone adaptive processes require usually no more than 2 or 3 years (Sievanen et al., 1996; Eser et al., 2004; Lang et al., 2006; Sibonga et al., 2007; Rittweger & Felsenberg, 2009), which is a shorter time period than the average of 5.5 years after surgery in this study. Future studies, with larger sample size and with longitudinal study design are required to address the question whether there is still a tendency towards recovery several years following ACL reconstruction.

We are aware of the fact that a relatively small number of subjects were enrolled in the present study. However, the study group is homogeneous in terms of undergoing the same surgical intervention, use of the same autograft and subjects had not undergone any other surgical intervention, or sustained any other serious injury to the studied limb. Also, the results are univocal, and statistically significant within the strict experimental conditions that we imposed. Finally, we are aware that different graft fixation means are available and in frequent use. We stress that the results in the present study are applicable only to patients who have received an ACL reconstruction using a PTB graft fixed with metallic interference screws. The use of other grafts (for example, hamstring tendons or quadriceps tendon patella bone graft), and other fixation screws such as bioabsorbable screws or a suspension device may well produce different results.

In conclusion, our results suggest that bone strength in the knee bones is permanently decreased after PTB surgery, even when muscle strength and patellar tendon stiffness are fully recovered (Reeves et al., 2009). The pertinent question therefore is which other mechanisms might constitute an effective limit to musculoskeletal forces. An obvious candidate from our study would be knee joint laxity, even though we found no correlation between laxity and side-to-side bone differences. Effective joint size has recently been proposed as another possible candidate (Rittweger, 2008), and, indeed, many ACL injuries present themselves in combination with chondral and meniscal damage, which are both likely to reduce the joint area available for force transmission. Unfortunately, this information has not been systematically assessed in the present study.

Finally, a second major conclusion to be drawn from the present study is that the signals to which tendon and muscle respond must be different from the signals that govern adaptive processes in bone. As reflected above, there is good evidence to

suggest that, for bone, strain magnitude (Rubin & Lanyon, 1985) and probably also strain rate (Mosley & Lanyon, 1998) play the most important role. Although forces are an important factor in the design of training regimens aiming at muscle hypertrophy, recent evidence suggests that work carried out (or energy dissipated) is likewise important, the latter being probably irrelevant for bone (Rittweger & Felsenberg, 2009). Of interest, strain magnitude seems to be the dominant factor that governs tendon adaptation, although other factors might be involved as well (Arampatzis et al., 2007).

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