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Original Article

Hylonome

Bone adaptation to altered loading after spinal cord injury: A study of bone and muscle strength

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Abstract

Bone loss from the paralysed limbs after spinal cord injury (SCI) is well documented. Under physiological conditions, bones are adapted to forces which mainly emerge from muscle pull. After spinal cord injury (SCI), muscles can no longer contract voluntarily and are merely activated during spasms. Based on the Ashworth scale, previous research has suggested that these spasms may mitigate bone losses. We therefore wished to assess muscle forces after SCI with a more direct measure and compare it to measures of bone strength. We hypothesized that the bones in SCI patients would be in relation to the loss of muscle forces. Six male patients with SCI 6.4 (SD 4.3) years earlier and 6 age-matched, able-bodied control subjects were investigated. Bone scans from the right knee were obtained by pQCT. The knee extensor muscles were electrically stimulated via the femoral nerve, isometric knee extension torque was measured and patellar tendon force was estimated. Tendon force upon electrical stimulation in the SCI group was 75% lower than in the control subjects ($p<0.01$). Volumetric bone mineral density of the patella and of the proximal tibia epiphysis were 50% lower in the SCI group than in the control subjects ($p<0.01$). Cortical area was lower by 43% in the SCI patients at the proximal tibia metaphysis, and by 33% at the distal femur metaphysis. No group differences were found in volumetric cortical density. Close curvilinear relationships were found between stress and volumetric density for the tibia epiphysis ($r^2=0.90$) and for the patella ($r^2=0.91$). A weaker correlation with the tendon force was found for the cortical area of the proximal tibia metaphysis ($r^2=0.63$), and none for the distal femur metaphysis. These data suggest that, under steady state conditions after SCI, epiphyseal bones are well adapted to the muscular forces. For the metaphysis of the long bones, such an adaptation appears to be less evident. The reason for this remains unclear.

Keywords: Disuse, Immobilization, Osteoporosis, Electrical Stimulation, Human Physiology

Introduction

The loss of bone from the paralysed limbs after spinal cord injury (SCI) is well documented. It occurs most rapidly in the first year after the onset of paralysis, slows down thereafter and eventually remains constant[1,2]. This decay is described accurately by a mono-exponential decline curve with a half-time between 1 and 1.5 years[2]. Interestingly, bones in the non-paralysed limbs of the same patients appear to remain unchanged[3-5]. It is generally accepted that bones have a capability to adapt to their mechanical usage. As a formal description of that adaptation in a cybernetic sense, Harold Frost has proposed the 'mechanostat' theory[6,7]. The theory suggests that strains within the bone are kept within certain limits by adding and removing bone tissue and thereby adapting the bone's strength to the forces exerted upon it.

Under physiological conditions, the largest such forces arise from muscle contractions. After SCI, sensory and motor functions are disrupted due to damage of the neural tissue within the spinal canal. However, in most cases this does not imply a complete loss of muscle contractions, as spasms and pathological spinal reflexes do frequently occur in most SCI patients. We therefore hypothesized that bone loss after SCI would be in relation to their ability to generate muscle force.

Whereas formerly, based on dual energy X-ray absorptiometry (DXA) measurements, it was reported that spasticity had no effect

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	Age [years]	Height [cm]	Weight [kg]	L_{Tibia} [cm]	L_{Femur} [cm]
SCI	35.7 (12.4)	186.7 (8.1)	82.7 (15.5)	40.4 (2.8)	44.8 (3.9)
AbleBodied	38.3 (12.8)	182.8 (8.0)	78.5 (8.9)	39.1 (2.1)	45.5 (3.5)

Anthropometric measures; L_{Tibia}=length of the tibia from the medial malleolus to the medial knee joint cleft; L_{Femur}=length of the femur from the lateral knee joint cleft to the greater trochanter.

Table 1. Subject characteristics.

upon the bone loss after SCI[8], a recent study with peripheral quantitative computed tomography (pQCT) conversely suggests that such an effect may indeed exist[9]. However, in that latter study muscle function was assessed very indirectly, namely by the Ashworth scale, which is a clinical score to assess 'spasticity'. It is therefore desirable to scrutinise the effects that muscle contractions may have upon the bones in SCI patients with a more direct technique.

Although patients with complete SCI lack the ability to contract sub-lesional muscles voluntarily, electrical stimulation can be used to elicit muscle contractions[10] and obtain a measure of muscle strength in these patients. On the other hand, it has been demonstrated that peripheral quantitative computed tomography can assess bone strength non-invasively[11-14]. To test our hypothesis, namely that bone strength in SCI patients is in relation to their reduced muscle forces, we have designed a study to compare muscle forces by electrical stimulation, and bone strength by pQCT, both in able bodied humans and SCI patients.

Materials and methods

Subject characteristics

Six male patients with SCI and six male age- and height-matched able bodied control subjects were investigated. They were included after giving their written informed consent to this study, which had been approved by the Ethics committee of the Vrije Universiteit, Amsterdam. The anthropometric characteristics can be seen in Table 1. In the patient group, SCI had occurred on average 6.4 years before (SD 4.3 years, span 2.6 to 13.6 years). In three patients, the level of spinal injury was C5, in one patient it was Th8, in one patient Th11 and in one patient L1. In three patients, the spinal lesion was complete. In two patients, there was some sensory function left, and one patient had some weak voluntary control left to the quadriceps muscle group. Five of the six patients had participated in a programme with functional electrical stimulation more than a year formerly[10].

Knee extension torque by electrical stimulation

All subjects participated in one experimental session with assessment of (electrically stimulated) contractile properties of the knee extensor muscles of the right leg. Before the start of the experiments subjects were familiarized with the test procedures.

Knee extension torque measurements were taken on the right leg at 90° knee angle (180°: full knee extension) on a custom-built computer controlled lower-limb dynamometer. The pelvis and the upper body were securely fixed to the seat, with the hip flexed at approximately 70° (0°=full extension). Precautions were taken to fasten effectively both the subject's upper body on the dynamometer's chair and the subject's leg on the application point of force on the dynamometer's lever. In the past, fractures have been observed when electrically stimulating muscles in SCI patients[15]. Hence, for safety reasons, the maximum knee-extension torque allowed to be produced by the SCI subjects was set at 75 Nm. In the event of the torque level exceeding this value, the lever arm would be released allowing the knee to extend. The lever arm could also be released if a safety button was pressed by the subject. This maximum torque was never reached by any of the SCI subjects.

Contraction of the quadriceps muscle was elicited by electrical stimulation (Digitimer DS7A, UK) through the femoral nerve. For this purpose two self-adhesive electrodes (Schwa-Medico B.V., Nieuw Leusden, the Netherlands) were used, the cathode in the femoral triangle over the femoral nerve (5x5 cm) and the anode (8x13 cm), distally over the medial part of the quadriceps muscle. A series of 3 square-wave pulses (triplet) of 0.2 ms duration each were delivered at 300 Hz. A full tetanic contraction by femoral nerve stimulation would produce a much higher knee extension torque than a triplet, but the high muscle forces generated might lead to bone fracture in the SCI patients[15]; hence this approach was avoided. To quantify the relation between the knee extension torque produced with our stimulation protocol (T_{trip}) and the torque produced by maximal activation of the quadriceps muscle (T_{MVC}), measurements of knee extension maximal voluntary contraction (MVC) were taken in five of the six control subjects examined. It was found that, at a 90° knee angle, TMVC was ~2.4 times larger than T_{trip} (absolute values 69 Nm, SD 11 vs. 163, SD 11 Nm).

Assessment of tendon force

To estimate the patellar tendon force from knee extension torque measurements, the patellar tendon lever length (PTLL) is required. This was quantified, in analogy to its assessment by videofluoroscopy[16] or by magnetic resonance imaging[17,18], from lateral scout images obtained by peripheral quantitative computed tomography (pQCT). An example

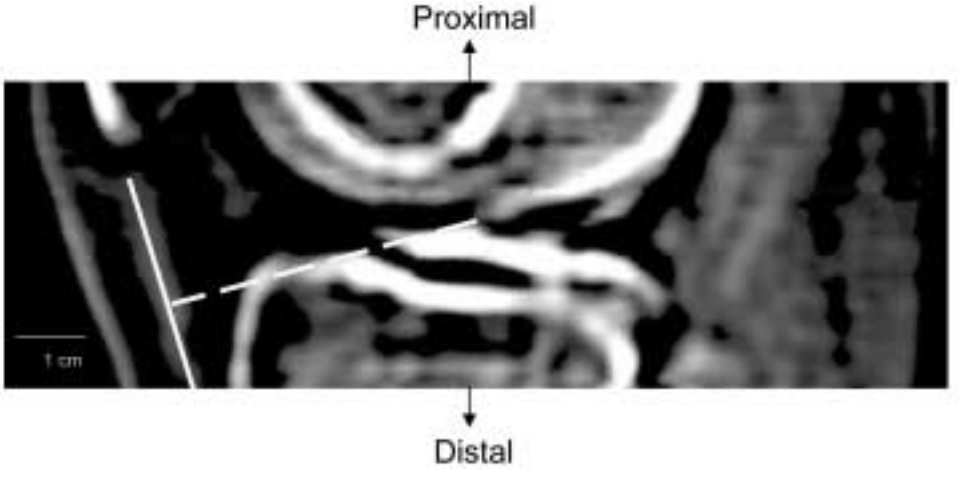

Figure 1. Example of a sagittal scout view image of the knee joint, depicting the femur epiphysis (top) and the tibia epiphysis (bottom). The edge of the patella can be discerned on the left upper edge, and the patellar tendon is marked by a solid line. The patellar tendon lever length is given by the dashed line, running perpendicular from the patellar tendon to the contact point between femoral condyl and tibia plateau.

is given in Figure 1. These images were obtained before taking bone scans (see below), using a XCT2000 (Stratec XCT 2000, Stratec, Pforzheim, Germany). Identification of the relevant anatomical structures on the images' scout views was carried out by two experienced operators. At first, the patellar tendon was identified as the opaque structure running from the patella down and in parallel to the skin. PTLL was then measured as the perpendicular distance of the tibio-femoral contact point to the patellar tendon action line (for accuracy of this approach see[19,20]). The patellar tendon force was computed as $F_{PT}=T_{Triplet}/PTLL$.

Peripheral quantitative computed tomography

Bone scans were performed by pQCT (machine details as above). Four scans were obtained from the right knee. After sagittal scout viewing and identifying the reference lines, one scan was performed at 5% of the tibia length from the proximal tibia plateau (tibia epiphysis=TibEpi, Figure 2) and one at 15% of the tibia length from the proximal tibial plateau (tibia metaphysis=TibMeta). Another scan was obtained at 15% of the femur length from the medial condylus (FemMeta). Finally, a mid-section scan was obtained from the patella. All scans were obtained with a voxel size of 0.5 mm edge length, with an X-ray slice thickness of 2 mm. The length of the tibia was assessed as the distance between the medial malleolus and the medial knee joint cleft. The length of the femur was assessed as the distance between the lateral knee joint cleft and the greater trochanter.

All pQCT scans were analysed with the integrated XCT software in its version 5.50 (Stratec Medizintechnik, Pforzheim, Germany). For the analysis of metaphyseal sites, the detection threshold for bone was set to 650 mg/cm^3. As the cortical shell in the tibia epiphysis and in the patella of the SCI patients was extremely thin, the detection threshold was set to 120 mg/cm^3 at these sites, and the regions of interest were drawn very tightly in order to avoid inclusion of soft tissue.

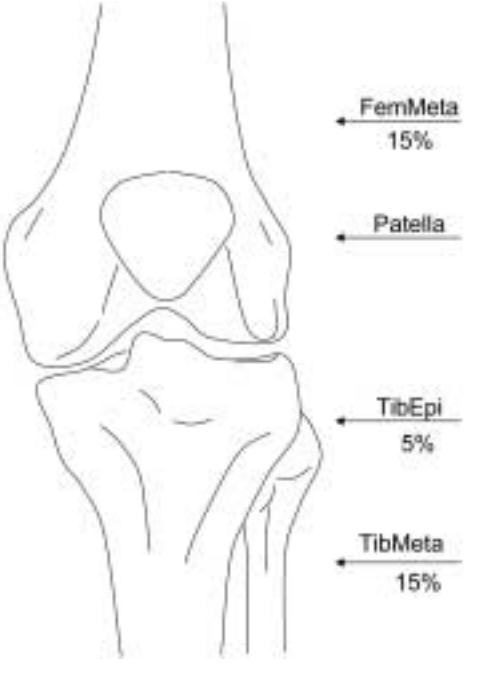

Figure 2. Illustration of the section levels at which peripheral quantitative computed tomography (pQCT was performed). Sectional images of the femur metaphysis (FemMeta) were obtained at 15% of the femur length, of the patella at 50% of its length, of the tibia epiphysis (TibEpi) at 5% of its length, and of the tibia metaphysic (TibMeta) at 15% of its length.

	T_{Trip} [Nm]	PTTL [cm]	F_{PT} [N]	$A_{Patella}$ [cm^2]	A_{TibEpi} [cm^2]	$A_{TibMeta}$ [cm^2]	$A_{FemMeta}$ [cm^2]	$\sigma_{Patella}$ [M Pa]	σ_{TibEpi} [M Pa]
SCI	24.5 (8.8)	4.00 (0.41)	612 (192)	5.83 (1.5)	31.3 (3.1)	10.1 (2.2)	11.4 (5.5)	1.13 (0.47)	0.198 (0.065)
Able Bodied	102.9 (33.4)	3.75 (0.07)	2620 (920)	7.50 (1.0)	34.6 (5.6)	13.0 (3.1)	12.3 (2.0)	3.58 (1.51)	0.784 (0.344)
p-value	**0.0003**	0.07	**0.001**	0.056	0.12	**0.044**	0.37	**0.010**	**0.009**
Ratio	23.8%	106.7%	23.4%	90.6%	90.6%	77.6%	93.4%	31.6%	25.3%

Group mean values and standard deviations of the knee extension moment upon electrical stimulation by a triplet (T_{Trip}), of the patellar tendon lever (PTTL), of the patellar tendon force (F_{PT}), of the total bone areas at the patella ($A_{Patella}$), tibia epiphysis (A_{TibEpi}), at the tibia metaphysis ($A_{TibMeta}$) and at the femur metaphysis ($A_{FemMeta}$), and of the stresses at the tibia epiphysis and the patella (σ_{TibEpi} and $\sigma_{Patella}$). The latter were computed from F_{PT} and $A_{Patella}$ and A_{TibEpi}, respectively. Significant group differences (in bold) were found for tendon force, $A_{TibMeta}$, $\sigma_{Patella}$ and σ_{TibEpi}. The ratio of the values from SCI patients and from the able bodied controls is given in the last row.

Table 2. Estimated tendon force and total bone areas.

	$BMC_{Patella}$ [$mg \cdot mm^{-1}$]	BMC_{TibEpi} [$mg \cdot mm^{-1}$]	$TotD_{Patella}$ [$mg \cdot cm^{-3}$]	$TotD_{TibEpi}$ [$mg \cdot cm^{-3}$]
SCI	146 (58)	397 (86)	273 (78)	126 (22)
Able Bodied	396 (46)	837 (96)	531 (91)	249 (59)
p-value	**0.000**	**0.000**	**0.001**	**0.006**
Ratio	36.7%	47.4%	51.4%	50.8%

Group means and standard deviation for the bone mineral content ($BMC_{Patella}$ and BMC_{TibEpi}) and total bone density at the patella ($TotDD_{Patella}$) and at the tibia epiphysis ($TotD_{TibEpi}$). Significant group differences (in bold) were found for all variables. The ratio of the values from SCI patients and from the able bodied controls is given in the last row.

Table 3. Bone results for tibia epiphysis and patella.

From the resulting database, we have extracted and analysed the values for:

- the total bone area of the tibia epiphysis (A_{TibEpi}), the tibia metaphysis ($A_{TibMeta}$), the femur metaphysis ($A_{FemMeta}$), and of the patella ($A_{Patella}$) in cm^2,
- the bone mineral content at the tibia epiphysis (BMC_{TibEpi}), at the tibia metaphysis ($BMC_{TibMeta}$), at the femur metaphysis ($BMC_{FemMeta}$), and of the patella ($BMC_{Patella}$) in g/cm,
- the total bone mineral density of the patella and the tibia epiphysis ($TotD_{Patella}$ and $TotD_{TibEpi}$, respectively) in mg/cm^3,
- the cortical area of the tibia and femur metaphyses ($A\_Crt_{TibMeta}$ and $A\_Crt_{FemMeta}$) in cm^2, assessed with a separation threshold of 650 mg/cm^3,
- the cortical bone mineral density at the tibia and femur metaphyses ($Rho_{TibMeta}$ and $Rho_{FemMeta}$) in mg/cm^3, which were adjusted for the partial volume effect according to (21), and
- the density weighted[a] polar moment of resistance[b] (so-called stress-strain index, SSI) of the tibia and femur metaphysis ($RP_{TibMeta}$ and $RP_{FemMeta}$, respectively) in cm^3.

The hypothetical peak stress during electrical stimulation at the tibia epiphysis (σ_{TibEpi}) and at the patella ($\sigma_{Patella}$) in Pa was computed by dividing F_{PT} by A_{TibEpi} and $A_{Patella}$, respectively.

Statistical analysis

Statistical analyses were carried out with the SPSS software version 11.5.0 (as of September the 6th 2002, www.spss.com). Student's t-tests were applied after checking for homogeneity

[a] Each voxel is weighted by its bone mineral density relative to a standard value of cortical density.

[b] The moment of resistance is also known as the section modulus.

of variances to test for differences between the SCI and able bodied subjects for all reported variables. Significance was accepted at $p<0.05$.

Stresses (σ_{TibEpi} and $\sigma_{Patella}$) and densities at the trabecular sections (patella and tibia epiphysis) were assumed to be related by a power function[11]. Accordingly, data were fitted to the function $\sigma_X=c \cdot DXa$, where X denotes either the patella or tibia epiphysis, σ is the stress and D is the density data. This was done with the Mathematica software in its version 4.1.2 (www.wolfram.com), performing a non-linear, least square fit.

Results

No group differences ($p>0.25$) were found in the anthropometric measures between the SCI and able-bodied subjects (Table 1). In the SCI group, both the peak knee extension torque and patella tendon force during electrical stimulation reached only about 25% of the values in the control group ($p\leq0.001$, Table 2). No substantial group differences between groups were found in the total bone areas. In consequence, the hypothetical peak stresses in the patella and at the tibia epiphysis in the SCI group were only 25-30% of those computed for the able bodied control group ($p\leq0.01$).

In the SCI group, BMC of the patella was 37%, and in the tibia epiphysis it was 47% of the BMC found in the able bodied control group. In both of these sites, the SCI group had a total bone density that amounted to about 50% when compared to the able bodied controls. All of these differences were highly significant (see Table 3). For both sites, fitting the hypothetical peak stresses to the total bone mineral densities by a power function yielded good results, with r^2 values of 0.90 and 0.91 (Figure 3a) and b)). This was true both with a pre-set exponent as well as for the optimised exponents. No correlation was found between the residuals of this relationship and the time since SCI.

For the metaphyses, group differences were generally smaller than for the tibia epiphysis and for the patella (Table 4). Only the group differences for BMC and cortical area in the tibia metaphysis were found to be significant, with the SCI group reaching about 55 to 60% of the values found for the control subjects. At the same site, the polar moment of resistance was 70% of the value observed in the able bodied controls. No group difference was observed for the polar moment of resistance of the femur metaphysis, although the BMC at this site in the SCI subjects was only 66% of the able bodied control subjects. Finally, cortical density was found to be almost identical between groups and sites.

Assessing the muscle-bone relationship for the metaphyses, regression analysis yielded a significant linear relationship between the patellar tendon force and the cortical area of the tibia (Figure 3c), but not of the femur.

Discussion

In the study sample, SCI had occurred more than 6 years before on average, and more than 2.6 years in each subject.

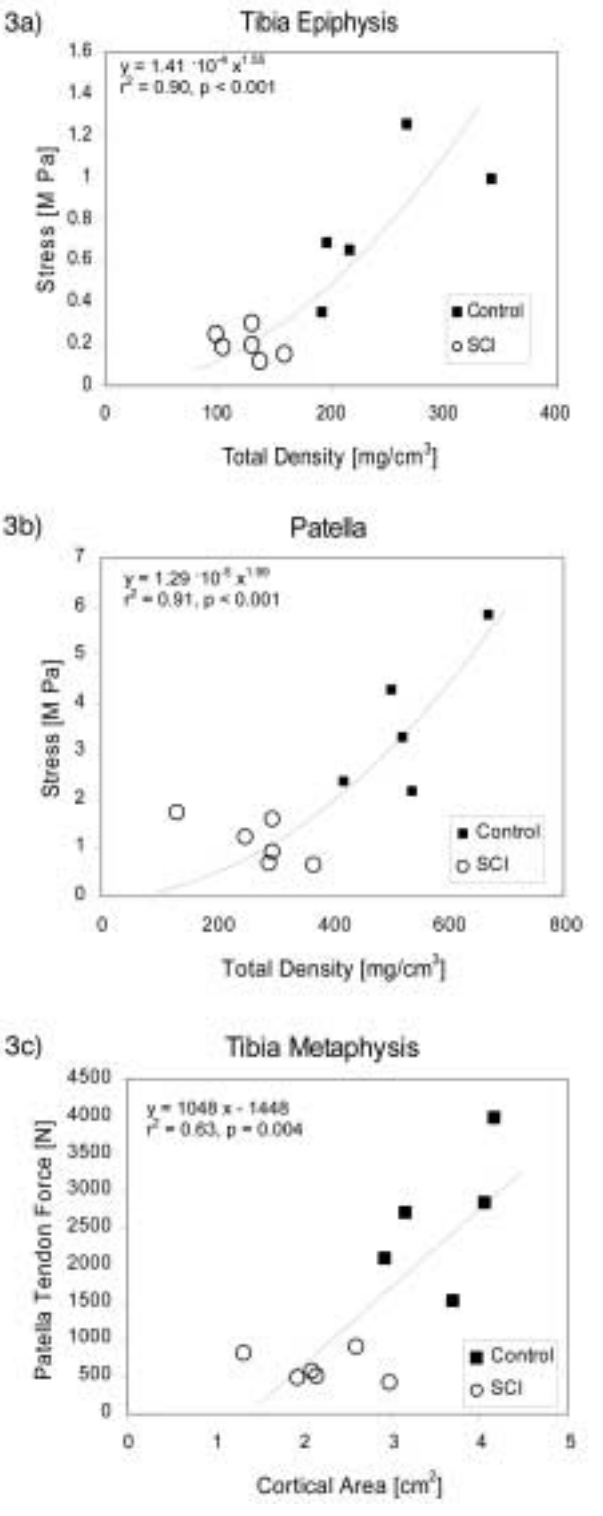

Figure 3a-c. Relationships between muscle and bone. For the tibia epiphysis (a) and the patella (b), the relationship is assessed by plotting the stress evoked by muscle contraction against the total bone mineral density as a surrogate of bone strength. For the tibia metaphysis (c), the relationship was assessed by patella tendon force and cortical bone area. In (a) and (b), stress and density values have been fitted to a power function, according to[11]. The good fit in a) and b) suggests that epiphyseal bone in SCI is adapted to the muscular force. For explanation see text.

	$BMC_{TibMeta}$ [mg·mm^{-1}]	$BMC_{FemMeta}$ [mg·mm^{-1}]	A_Crt_{ibMeta} [cm^2]	$A\_Crt_{FemMeta}$ [cm^2]	$Rho_{TibMeta}$ [mg·cm^{-3}]	$Rho_{FemMeta}$ [mg·cm^{-3}]	$RP_{TibMeta}$ [cm^3]	$RP_{FemMeta}$ [cm^3]
SCI	322 (115)	349 (195)	2.04 (0.68)	2.07 (1.28)	1151 (59)	1187 (46)	7.87 (2.40)	10.8 (5.6)
Able Bodied	550 (60)	531 (66)	3.61 (0.54)	3.09 (0.21)	1142 (55)	1201 (29)	11.3 (4.00)	10.6 (2.8)
p-value	**0.001**	0.055	**0.002**	0.056	0.80	0.58	0.050	0.49
Ratio	58.6%	65.8%	56.5%	67.0%	100.8%	98.8%	69.6%	100.9%

Group means and standard deviations for the bone mineral content ($BMC_{TibMeta}$ and $BMC_{FemMeta}$), for the cortical area ($A\_Crt_{TibMeta}$ and $A\_Crt_{FemMeta}$), of the cortical density ($Rho_{TibMeta}$ and $Rho_{FemMeta}$), and of the density weighted polar moment of resistance at these sites ($RP_{TibMeta}$ and $RP_{FemMeta}$) at the tibia metaphysis and at the femur metaphysis. Significant group differences are given in bold.

Table 4. Bone results for the metaphyses.

Hence, according to the findings of Eser et al.[2], we would expect the bones of the SCI patients to be in a steady state.

Our analysis has yielded that, as compared to the able bodied controls, the SCI patients had only (i) 25% of the patellar tendon force with electrical stimulation, (ii) still about 50% of the bone mass at the trabecular sites, and (iii) about 60-70% of the bone mass and the cortical area at the metaphyseal sites. Conversely, there was no substantial group difference in the patella tendon lever arm or in the total bone area, i.e., the outline of the epiphysis, metaphysis and patella. Also, there was no group difference in cortical density of the metaphyses. These observations are compatible with the interpretation that SCI changes neither the shape of bones nor the compartmental[22] bone density, but that bone loss occurs through endocortical resorption in cortical bone, and through reduction of the trabecular network in cancellous bone. These findings are in line with previous studies[2,23].

This study involves three novel approaches in the analysis of the muscle-bone relationship, namely (a) the utilisation of electrical nerve stimulation, (b) the assessment of tendon force, and (c) the comparison of surrogate measures for stress vs. density, rather than force vs. mass or torque vs. moment of resistance, as opposed to former studies[24-26]. Doing so, a curvilinear relationship was found that could be well fitted to a power function (Figure 3). The nature of this power relationship has been established for the ultimate strength of iliac crest biopsies, where an exponent of 2.6 was found for specimens from male subjects[11]. Our fitting procedures yielded somewhat different exponents (Figure 3), which may be explained by different bone sites experiencing different strain patterns.

It appears, thus, as though the reduced strength of both the patella and the tibia epiphysis of the SCI patients was in relation to the loss of muscular forces, as extrapolated from the data of the able bodied control group. For the tibia metaphysis, that muscle-bone relationship was less strong, and for the femur metaphysis, no significant correlation at all was found between bone strength and muscle force. This suggests that, after SCI, the metaphyses follow a trend that diverges from the tibia epiphysis and the patella. This divergence may also be exemplified by the amount of bone loss – the relative group differences for patella and tibia epiphysis were about twice as large as for the metaphyses. Such differences, both in the initial rate of loss[8,27] but also after the bone loss has come to a stop[2,3] have been reported previously. As a rough figure, about 50% of the epiphyseal bone mineral is removed after SCI, but only 30% in the shafts of the long bones[2]. Usually, that difference is attributed to a biologically different behaviour of the two tissue types, namely cancellous bone at the epiphyseal sites as opposed to compact bone in the shafts. Our data may contradict this notion, as some parts of the patella are usually made of compact bone. However, the group differences for the patella, as well as the muscle-bone relationship (Figure 3) were very similar to the findings for the tibia epiphysis. Therefore, an alternative explanation is warranted.

The loading of bones usually causes complex strain patterns, encompassing e.g., variable amounts of e.g., bending and compression. Possibly, the relative contributions of uniaxial loading versus bending and torsion patterns of the leg bones are altered as a result of SCI (in favour of the latter two). It is noteworthy in this context that fractures are not uncommon in patients with SCI. In fact, the lifetime risk of an SCI patient for lower limb fracture is twofold increased as compared to able bodied humans[28]. These fractures typically occur most at the metaphyses of the knee[29] during care activities or transfer – when bending and torsion moments accidentally emerge.

It could be argued that the reduction in muscle strength would not be the cause, but rather a parallel to the reduction in bone strength after SCI, as there is accumulating direct evidence for an involvement of the central nervous system in bone metabolism[30,31]. Such nervous influence is probably best understood for the sympathetic nervous system, which is thought to hamper bone formation and stimulate bone

resorption[32]. However, sympathetic nerve activity is decreased after SCI, and, accordingly one should expect increases in bone mass and strength via this pathway. On the other hand, intramuscular injection of botulinus toxin A, an agent which is highly specific to block neuromuscular transmission reduces muscle strength and bone mass in mice[33]. Hence, there is a growing body of evidence, too, to underpin a causal involvement of muscular impairment in bone loss. Hopefully, the present study may contribute hitherto by suggesting that epiphyseal BMD in SCI patients is more or less where it would be expected from the observations in able bodied people.

This study has two limitations. Firstly, the sample size is small. The study was originally designed to find group differences, and the sample size was limited for ethical implications (electrical stimulation). When analysing the data, however, we found the close relationship reported in Figures 3a) and 3b). Obviously, these relationships do not constitute decisive results, but rather contain an interesting observation. Future studies have to show whether these close muscle-bone relationships are due to the more objective assessment of muscle strength by electrical stimulation, or whether they are an effect of the more elaborate biomechanical approach (patella tendon force, relating a surrogate of stress with density). Secondly the design was cross-sectional. Rather than comparing SCI patients to able bodied control subjects, one would wish to investigate the same SCI patients repeatedly in order to tease out inter-individual variation, which is crucial in immobilization-induced bone loss[34]. However, bones and muscles have different response times[35]. Whereas muscle atrophy commences rapidly and is nearly complete after 17 months[36], bone loss goes on for several years. The only steady state conditions where the bone-muscle relationship might be established would therefore be before and after the spinal cord injury. It is self evident that that such a study is almost impossible to do in humans.

In conclusion, this study has shown that, after spinal cord injury, the bone losses in the patella and in the proximal epiphysis of the tibia appear to be in relation to the knee extensor forces. To a certain extent, this is also true for the tibia metaphysis, but not for the femur metaphysis. The reasons for this obvious divergence remain unclear.

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Another study on the very same participants has recently been published[37].

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