Musculoskeletal Interactions in Normal Subjects and Dialysis Patients

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INTRODUCTION

Age-related fracture risk depends on both reduced bone strength and an increased propensity for fall-related trauma (1). Bone strength depends not only on the quality and amount of its constituent material (hydroxyapatite and organic matrix) but also on the micro- and macro-architectural distribution of that material (2). While the quality of the material is constant in physiologic conditions, its amount and distribution, i.e. the bone geometry, is uneven in different bone segments and depends closely on the history of the peak loads on it (2,3).

The importance of bone geometry as well as bone mass as determinant of appendicular fracture risk is well recognized (4,5) ; moreover, the results of a recent ex vivo study even suggest that pQCT derived cross-sectional geometry parameters are better predictors of bone strength than volumetric cortical and trabecular density or cortical area, a measure of bone mass (6).

Biomechanical strength parameters, noninvasively obtained by pQCT, have been proposed and validated (7) ; they are obtained multiplying the volumetric cortical density by the cross-sectional moment of inertia (Bone strength index or BSI) or with the section modulus, a parameter derived from the moment of inertia which also takes into account the eccentricity of bone material (Stress-strain index or SSI). The BSI proved superior to either cortical density or cross-sectional moment of inertia alone, and to DXA measured areal density, in predicting fracture loads in rat femurs (7), and the SSI provided a good separation between patients with Colles' fracture and non fractured controls (8).

Renal osteodystrophy is uniformly present in uremic patients on maintenance hemodialysis (9); however, although in previous studies employing absorptiometry methods the presence of osteopenia in cortical bone rich sites has been reported, in none of them the issue of bone fragility in this condition has been specifically addressed (10,11). By means of pQCT, which permits to assess cortical and trabecular bone density separately as well as to non-invasively evaluate the geometrical properties of long bones, cortical osteopenia and geometry impairment has been reported at the distal radius of uremic patients on maintenance hemodialysis (12).

In the uremic patients on maintenance hemodialysis a reduced muscle mass and strength (sarcopenia) is a prominent clinical feature (13). Muscle force has been shown to be a major determinant of the SSI and it has been suggested that a significant deviation from linearity in the relationship between muscle force and SSI could be useful to differentiate osteopenia caused by decreased muscle strength (for instance disuse osteopenia) from conditions which lead to inadequate adaptation of bone to

	Males	*Females*
Controls	1107.4±*24*	1090±*33.8*
Dialysis	1036.6±*193*	1035±*65.4*
p values	0.04	0.0002

Table 1
Comparison of Cortical bone density values between male and female dialysis patients and controls.

mechanical usage (8).

Muscle cross-sectional area, which is known to be correlated to muscle force, can be non-invasively measured by means of a new pQCT machine (14).

In this study the muscle and bone cross-sectional area, along with the the cortical bone density and the SSI, have been evaluated in a group of dialysis patients and, by comparison, in an age-matched control group with the purpose of confirming the existence of cortical osteopenia and sarcopenia in these patients, and of assessing whether or not the osteopenia can be entirely explained by the concomitant sarcopenia.

SUBJECTS AND METHODS

Study subjects

64 dialysis patients (33 males, 31 females, mean age ±SD : 65.8 ±14 and 68.6 ±13 years, respectively) and 64 age-matched healthy controls (33 males, 31 females, mean age±SD : 66.2 ±13 and 68.4 ±13 years, respectively) have been evaluated. The dialysis group was recruited without prior selection from the population of uremic patients on maintenance hemodialysis attending the hospital dialysis Unit. The control subjects were physically active individuals recruited from the community dwelling population. Any disease or condition capable of interfering with bone metabolism or active lifestyle and intake of drugs known to influence bone metabolism were considered exclusion criteria.

In order to insure that the dialysis group was really non-selected as to age or severity of disease, all the measurements have been made at the patients' bedside during the dialysis session, while the control subjects were evaluated at the osteoporosis outpatient clinic.

Methods

All the pQCT measurements have been performed with the XCT 2000 (Stratec Gmbh, Pforzheim, Germany), a new machine capable of measuring muscle cross-sectional area at the lower leg as well as performing trabecular and cortical measurement at both the forearm and lower leg (14).

The distal end of the tibia was used as an anatomical marker ; the bone cross-sectional area (BA) has been measured at 14%, 38%, and 66% of the tibia length, proximal to

	Control	Dialysis	*Diff.*	p.value
Polar SSI (mm³)	**1692** *±281*	**1294** *±375*	397	<0.0001
X-axis SSI (mm³)	**943** *±166*	**751** *±187*	192	<0.0001
Y-axis SSI (mm³)	**974** *±152*	**766** *±182*	209	<0.0001

Table 2a
Comparison of SSI values (14% proximal of tibia end) between male dialysis patients and controls.

	Control	Dialysis	*Diff.*	p value
Polar SSI (mm³)	**1042** *±197*	**815** *±209*	226	<0.0001
X-axis SSI (mm³)	**580** *±20*	**455** *±19*	125	<0.0001
Y-axis SSI (mm³)	**597** *±107*	**450** *±130*	146	<0.0001

Table 2b
Comparison of SSI values (14% proximal of tibia end) between female dialysis patients and controls.

this point. The cortical bone density was measured at the 38% site only, where an interference on the measurement results by the partial volume effect is prevented by the cortical shell thickness. The SSI (polar-, X-axis-, and Y-axis-SSI) was calculated at the 14% and at the 38% site ; however, only the results of the 14% site, mostly affected by the mechanical loads on the tibia, are shown. The muscle cross-sectional area (MA) was measured at the junction of the proximal third with the middle third of the tibia (the 66% site). The separation between subcutaneous fat and muscle was performed by a mixed manual and threshold technique. The details of bone density and cross-sectional area measurement, as well as the calculation of the SSI, have been reported elsewhere (8).

RESULTS

The cortical bone density was reduced in the dialysis patients in comparison with the control subjects ($p=0.0002$ and $p=0.04$ for the female and male patients, respectively), confirming previous results (Table 1).

In comparison with the control subjects, the SSI (polar-, X-axis-, and Y-axis-SSI at the 14% site) was reduced in both the male and female patients ($p< 0.0001$ for all the comparisons) (Tables 2a and 2b).

Compared with the control subjects, both MA and BA were significantly reduced in the dialysis patients of both sexes (p values < 0.0001 for all the comparisons); however, the ratio of MA to BA was strikingly increased in the female patients only ($p< 0.0001$, a three fold increase) and unchanged in the male patients (Tables 3a and 3b).

In the control subjects a highly significant relationship was found between MA at 66%

	MA (mm^2)	*BA* (mm^2)	*MA/BA*
Controls	*75.2* ±*10.2*	*377.1* ±*63,7*	*19.6* ±*4.7*
p values	*<0.0001*	*<0.001*	*0.4 (N.S)*
Dialysis	*55.1* ±*15*	*315.1* ±*78*	*18.6* ±*5*

Table 3a
Comparison of Muscle Area (MA), Cortical Bone Area (BA), and ratio of Muscle Area to Cortical Bone Area (MA/BA) between male dialysis patients and controls.

	MA (mm^2)	*BA* (mm^2)	*MA/BA*
Controls	*60.4* ±*10*	*263.3* ±*65.5*	*23.3* ±*5.2*
p values	*<0.0001*	*<0.0001*	*<0.0001*
Dialysis	*45.8* ±*9.2*	*174.8* ±*7.7*	*66.4* ±*13.4*

Table 3b
Comparison of Muscle Area (MA), Cortical Bone Area (BA), and ratio of Muscle Area to Cortical Bone Area (MA/BA) between female dialysis patients and controls.

and BA at the three measurement sites (r values between 0.58 and 0.67, p values between 0.0006 and <0.0001). In the dialysis patients a relationship between MA and BA was still present, albeit with lower r values (between 0.27 and 0.55), which not always reached statistical significance (Tables 4a and 4b).

By visual inspection of the graphical plot of the data a profound gender difference in the musculo-skeletal interaction is evident in the dialysis patients. In fact, while in the male patients only a leftward displacement of the data points was observed, the female patients presented a downward as well as a leftward displacement (Figures 1a and 1b), indicating a more severe impairment in the relationship between muscle and cortical bone cross-section.

In the control group, the MA/BA ratio showed no age-dependent change in the males, and a significant increase in the postmenopausal females, while in the dialysis group, no significant age-dependency was observed in either sex (Figures 2a and 2b).

DISCUSSION

In this study the presence of cortical osteopenia and bone fragility in the dialysis patients of both sexes has been confirmed. Moreover, the results show the presence of sarcopenia in the patients of both sexes, a weaker dependency of the bone cross-sectional area from the muscle cross-sectional area, and a clear-cut higher degree of osteopenia relative to the sarcopenia in the female patients, compared with the males.

The relative and the absolute or attributable risk for hip fracture has recently been shown to be greatly increased in the dialysis patients in both sexes in a U.S. nationwide epidemiological study by Gupta et al. (15) ; therefore, the presence of cortical

	Males		*Females*	
	r	p	r	p
C.Area T+F 14%	0.61	0.0003	0.67	<0.0001
C.Area Tibia 38%	0.64	0.0001	0.58	0.0006
C.Area T+F 66%	0.66	<0.0001	0.58	0.0006

Table 4a
Relationship of Muscle Area with Cortical Bone Area at different distances from the distal tibia end in male and female controls.

	Males		*Females*	
	r	p	r	p
C.Area T+F 14%	**0.27**	0.1 (NS)	**0.55**	0.0016
C.Area Tibia 38%	**0.24**	0.2 (NS)	**0.51**	0.0041
C.Area T+F 66%	**0.37**	0.0321	**0.52**	0.0034

Table 4b
Relationship of Muscle Area with Cortical Bone Area at different distances from distal tibia end in male and female dialysis patients.

osteopenia and a clear-cut reduction in the index of bone strength may have practical as well as speculative relevance. In fact, based on both the present data and those reported by Gupta et al. (15), appendicular fracture prevention should be included in the clinical management of these patients. Moreover, it is suggested to evaluate in prospective studies the assessment of the SSI as a means of predicting fracture occurrence and guiding treatment decisions in these patients.

In this study the cross-section of muscle and cortical bone have been measured at the proximal third of the lower leg of the uremic patients on maintenance hemodialysis. It is known from the literature and is commonplace in the clinical practice to observe sarcopenia in the dialysis patients (18) ; therefore, theoretically the observed cortical osteopenia could be the appropriate homeostatic response of bone to a reduction in mechanical usage and attendant reduction in prevalent strains. However, in a secondary bone disease like renal osteodystrophy a disturbance in the adaptive response of bone mass to a change in muscle force is also conceivable, and according to the initial hypothesis of this study, would be detectable as a change in the relationship between muscle and bone cross-sectional area. The results show that this is indeed the case. In fact, the relationship between MA and BA was weaker in the patients than in the controls suggesting the presence of an interfering pathogen. From the current knowledge of the pathophysiology of renal osteodystrophy, it may be suggested that the persistent elevation of PTH levels with its attendant activation of bone resorption may be responsible for the observed musculo-skeletal imbalance (16).

In the cited study of Gupta, although the relative risk of hip fracture was excessive in the dialysis patients of both sexes, the absolute risk was considerably higher in the female patients; in other words, a greater percentage of female than male patients sustained hip fracture. Again, this study provides evidence of a possible underlying mechanism. In fact, the results show a greater degree of osteopenia relative to

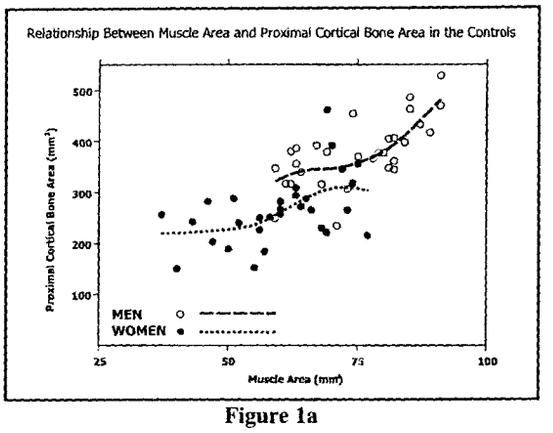

Figure 1a

sarcopenia in the female patients compared to the males, suggesting the interference of a further pathogenic factor on the muscle-bone relationship, only present in the female sex.

According to the feed-back model proposed by Frost (3,17), bone mass and cross-sectional geometry are regulated by the load derived strains. When loads, and hence strains, decrease below a certain threshold, remodeling is activated to remove the perceived "excess" bone from the endocortical surface, while, following an increase in strains, periosteal and trabecular modeling increase mass and cross-sectional area keeping strains within safe limits, which means improving resistance to fracture. A variety of agents can modify the strain thresholds, the most important being the estrogens which are known to lower the amount of strain necessary to stop the remodeling process (17); at low estrogen level, as in the postmenopausal state, remodeling removes bone at higher strain levels. A lifelong estrogen deficiency, reported in the literature (18) and clinically evident in all the dialysed women, may be the pathogenic factor responsible for a greater degree of osteopenia relative to sarcopenia in the female patients.

In conclusion, the dialysis patients present weak muscles, fragile bones, and an

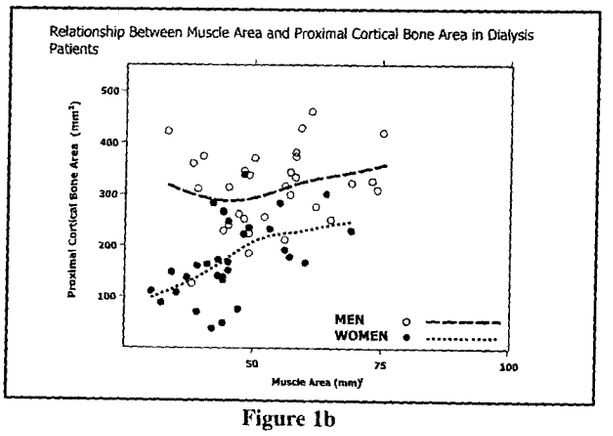

Figure 1b

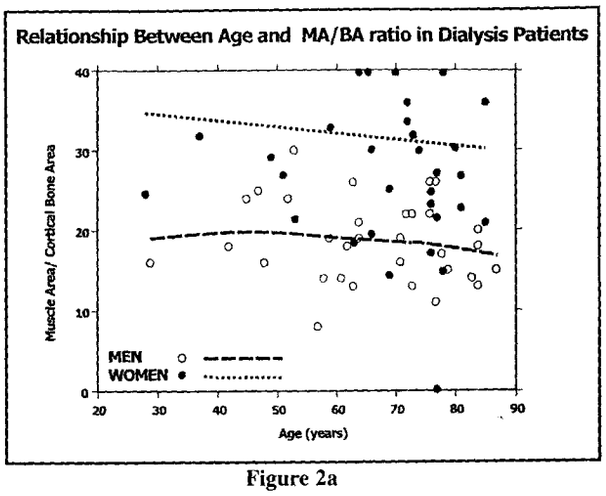

Figure 2a

impaired adaptation of bone strength to mechanical usage; since these alterations result in an increased appendicular fracture risk, preventive treatment would seem appropriate. In particular, the female patients should be offered treatment with estrogens. The assessment of cortical bone density, cortical bone area, the SSI and the ratio of muscle to cortical bone area should be further evaluated as a means of predicting fracture risk and guiding treatment decisions in dialysis patients. The ratio of muscle to cortical bone area appears to be a promising tool for the differention of disuse osteopenia from secondary osteopenias.

CONCLUSIONS

Muscle force is a major determinant of bone mass and strength. The purpose of the study was to assess the interaction between the muscle cross-sectional area (M-CSA),

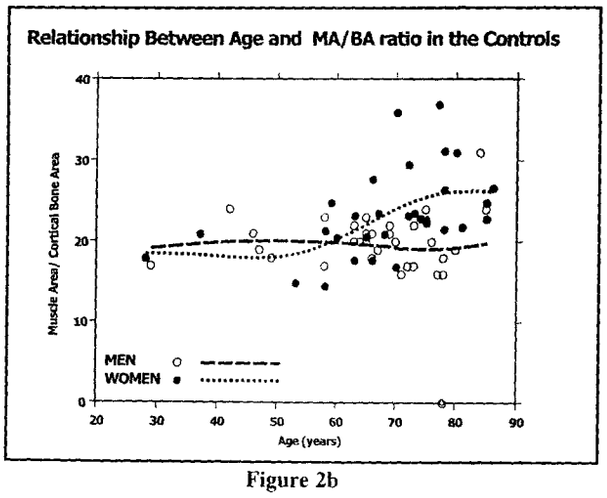

Figure 2b

an indicator of muscle mass and force, and the cortical bone cross-sectional area (B-CSA), an indicator of bone mass and strength, in hemodialysis patients and age-matched controls.

M-CSA and B-CSA were assessed at 66%, volumetric cortical bone density (vCD) at 38%, and the Stress-strain index (SSI) at 14% of the tibia length, from the distal tibia end, by means of peripheral Quantitative Computed Tomography (Stratec XCT 2000).

vCD was reduced in both male ($p < 0.05$) and female ($p < 0.001$) dialysis patients. The SSI was reduced in the patients ($p < 0.0001$ in both sexes). In the controls, a good correlation was observed between M-CSA and B-CSA ($r = 0.66$, in the males, $r = 0.58$ in the females ; $p < 0.0001$ in both sexes) ; moreover, both M-CSA, and B-CSA, along with SSI, significantly declined with ageing in both sexes; in the patients, M-CSA, B-CSA, and SSI were reduced in both sexes compared with the controls ($p < 0.0001$ for all the comparisons). The M-CSA/B-CSA was consistent with age in the male controls, but increased in the females after the 5th decade, a possible effect of estrogen deficiency. The female patients showed higher M-CSA/B-CSA than either male patients or controls of both sexes ($p < 0.0001$ for all the comparisons), presumably a consequence of life-long estrogen deficiency.

In conclusion, M-CSA and B-CSA are related to each other and decline with age in the normal subjects, along with SSI. The dialysis patients of both sexes show weak muscles (low M-CSA) and poor quality (low vCD), fragile bones (low B-CSA and SSI). In the female sex, the increase in the M-CSA/B-CSA found in all the patients and in the postmenopausal controls suggests an important role for the estrogens in the musculo-skeletal interaction. Estrogen treatment should be considered for the female dialysis patients. The M-CSA/B-CSA might prove useful in the future for the evaluation of other osteopenic conditions.

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