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Original Article

A Cybernetic approach to osteoporosis in Anorexia Nervosa

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Abstract

A group of 25 female individuals, who had been admitted to the University Hospital with the diagnosis of anorexia nervosa (AN) 3 to 10 years before, was seen for a follow-up visit in the hospital. These women got a psychiatric exploration to detect a present eating disorder. Moreover, parameters of the muskuloskeletal interaction were determined on the non-dominant forearm. Bone mineral content (BMC) of the radius was measured by pQCT and maximal grip force was evaluated by the use of a dynamometer. Eating disorders were present in 12 females. The mean of BMC standard deviation (SD) score was significantly reduced in comparison with reference values. Furthermore, the mean of BMC SD score was also significantly lower than the mean of grip force in SD score. These results gave the suggestion that the adaptation of bone mass to biomechanical forces is disturbed in AN. The linear regression analyses between the parameters grip force and BMC were compared between the study and the reference group. The comparison delivered a significantly lower constant in the regression equation of the study group. This result can be interpreted on the background of the mechanostat theory. The affection with an eating disorder decreases the set point in the feedback loop of bone modeling. The results offer for the first time the possibility to analyse osteoporosis in anorexic females under the paradigm of muskuloskeletal interaction.

Keywords: Anorexia Nervosa, Osteoporosis, Bone Mineral Content, Grip Force

Introduction

Anorexia nervosa (AN) is a typical disease of the adolescent female and comes up with a prevalence of 1% in western societies[1]. The fear of being fat, self-imposed semi-starvation and endocrine dysfunction are typical symptoms of AN. About one half of patients with AN experience secondary amenorrhea concomitant with the onset of dieting, whereas in one-fifth menses disappear before the onset of overt disease. The remaining patients undergo secondary failure of menses after the weight loss is significant[2,3].The absence of gonadal hormones is suspected as an important pathogenetic factor for the susceptibility of osteoporosis in anorexic individuals[4-6]. A previous study mentioned a benefit of estrogen replacement therapy (ERT) for the prevention of osteoporosis in anorexic females[7].

A view on the adaptation of bone mass due to biomechanical forces delivers a conceptual issue, why amenorrhea and osteoporosis might be related in anorexic women. Muscle force and forces related to the gravitation field provide the biomechanical environment of the bone[8]. Muscular inactivity leads to reduced mass of muscle fibres which is called muscle atrophy or sarcopenia. The adaptation of bone to sarcopenia results in osteopenia, which facilitates typically located osteoporotic bone fractures[9-11]. Therefore, resistance exercise is thought to provide the necessary mechanical stimuli to maintain or to increase bone mass protecting the skeleton from bone fractures[12,13]. Modeling of the bone is modulated by endocrine mechanisms. For example, estrogens modulates the adaptation of bone to biomechanical stress[14]. In conclusion, on the one hand bone mass is increased by the extension of mechanical forces on the skeleton, and on the other hand bone mass is raised due to the amplification of mechanical signals as it is discussed for the biological effect of estrogens.

This study is a cross-sectional investigation about parameters describing bone mass, anthropometric characteristics and muscle force in females with a present eating disorder or

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List of Abbreviations

AN	anorexia nervosa
ERT	estrogen replacement therapy
EE	ethinylestradiol
pQCT	peripheral computed tomography
BMI	body mass index
BMC	bone mineral content
vBMDtot	volumetric total bone mineral density
vBMDtrab	volumetric trabecular bone mineral density
SD score	standard deviation score
y	year

a former episode of AN. The special issue of the present study is focused on the relationship between bone mass and muscle differences between women affected with AN and healthy females of a reference population. Because bone strength is dependent on bone mass, the answer to this question opens a view into the cybernetic relationship between bone mass and muscle force in AN. Therefore, this issue reveals new aspects for the pathogenesis of osteoporosis in AN and might explain why ERT can have a beneficial force. The hypothesis of this study says that the adaptation of bone strength to muscle force is not for the prevention of osteoporosis in AN.

Methods and subjects

Subjects

Seventy-one females, who had required admission to the University Hospital of Child and Adolescent Psychiatry with the diagnosis of restrictive AN (ICD-10 F50.0) more than 3 years before, were asked to contact the hospital for a follow-up visit[15]. Finally a group of 25 former patients took part in this cross-sectional investigation. They had required admission to the hospital 6.4±2.0 y (range 3.3 – 10.2 y) before. The primary admission to the hospital had been at the age of 15.0+1 y (range 12 – 17 y).Psychiatric therapy was provided on average for 2.2+1.1 y (range 1-7 y). At the day of follow-up visit 12 females were still affected by an eating disorder, but none of them was actually under psychiatric therapy. In 4 females restrictive AN was still present. The transition from restrictive AN to bulimia nervosa appeared in 7 cases (to typical bulimia nervosa in 4 cases (ICD-10 F50.2), to atypical bulimia nervosa in 3 cases (ICD-10 F50.3)). The eating disorder was classified as non-specific (ICD-10 F 50.9) in one individual.

All individuals were asked for menarche, amenorrhea and the use of drugs containing estrogens. Menarche had appeared at the age of 13.0+1.6 y (range 11-18 y). The start of amenorrhea had been at the age of 15.2+1.7 y (range 12-21 y). Only one female suffered from a primary amenorrhea. The duration of amenorrhea was 2.1+1.9 y (range 0.5-9.7 y). At the day of follow-up visit, amenorrhea was present in only one female and contraceptive drugs containing estrogen were still being used by 11 females. 20 females had been treated with estrogens since the start of AN. Ethinylestradiol (EE) had been applied in all cases. Females were asked for the dose of EE and as well for the period of treatment with EE. The cumulative dose was 205.5+183 mg (range 3,1-1895,2 mg) per individual over 3.0+2.4 y (range 0.5-7.0 y) of treatment.

The stage of pubertal development was determined by physical examination using the grading system defined by Tanner for pubic hair[16]. Tanner stage 4 was present in 3 females, Tanner stage 5 was seen in 22 females.

The study was approved by the Ethics Committee of the University, and informed consent was obtained from all patients.

Evaluation of muscle force and bone parameters

Parameters of bone density of the radius of the non-dominant side were measured by peripheral quantitative computed tomography (pQCT) (XCT 900; Stratec Medizintechnik GmbH, Pforzheim, Germany). A single tomographic slice of 2.5 mm thickness was taken at the site of the radius whose distance to the medial border of the distal radial articular cartilage corresponded to 4% of forearm length. Forearm length was measured as the distance between the ulnar styloid processus and the olecranon using a caliper. Volumetric total bone mineral density (vBMDtot), bone mineral content (BMC) and volumetric trabecular bone mineral density (vBMDtrab) were automatically analysed from the tomographic image using the manufacturer's software (version 5.20). vBMDtrab was defined as the mean mineral density of the 45% core area of the bone's cross-section. BMC closely corresponds to the mass of mineral contained in the entire tomographic slice. Therefore, BMC is a useful parameter to represent bone mass. The parameters BMC and vBMDtrab were converted to XCT 2000 reference values as it has been described by Rauch et al. vBMDtot values were not converted to XCT 2000 reference values because this conversion is methodologically impossible[17]. Converted values were used for the construction of SD scores for BMC and vBMDtrab.

Maximal isometric grip force of the non-dominant hand was determined with a standard adjustable-handle Jamar dynamometer (Preston, Jackson, MI, USA). The subjects were seated with their shoulder adducted and neutrally rotated. The dynamometer was held freely, without support. The elbow was flexed at 90° and care was taken that it did not touch the trunk. The forearm was in a neutral position, the wrist was held at between 0° and 30° dorsiflexion and

Table 1. Anthropometric characteristics and results of musculoskeletal analyses in the entire study population.

	Mean ± SD	Median	Range
Age (y)	22.0 ± 2.3	21	19 – 26
Height (cm)	167 ± 7	168	154 – 181
Weight (kg)	55 ± 11	54	32 – 79
BMI (kg/m^2)	19 ± 2	19	13 – 23
vBMDtot (mg/cm^3)	252 ± 47	251	116 – 362
vBMDtrab (mg/cm^3)	129 ± 34	131	54 – 187
BMC (mg/mm)	90 ± 15	93.8	46 – 115
Grip Force (N)	302 ± 47	294	226 – 412
SD scores			
Height	-0.2 ± 1.0	-0.2	-2.1 – 1.6
Weight	-0.7 ± 0.9*	-0.7	-2.6 – 1.7
BMI	-0.7 ± 1.0*	-0.8	-2.9 – 2.3
vBMDtrab	-0.9 ± 0.9*	-0.9	-2.8 – 0.8
BMC	-0.8 ± 1.0*	-0.5	-3.6 – 0.8
Grip Force	0.2 ± 0.9	0.2	-1.2 – 1.9

The asterisk denotes a significantly lower mean in SD scores than zero ($p<0.05$). The other mean SD scores were not significantly lower than zero ($p>0.2$).

Table 2. The follow-up collective is divided into still affected females and actual recovered women regarding the presence of an eating disorder.

	Mean + SD	
	Eating Disorder (N=12)	Recovered
(N=13)		
Age (y)	21.6 ± 2.1	22.2 ± 2.5
Height (cm)	164 ± 7	169 ± 6
Weight (kg)	50 ± 12	58 ± 6
BMI (kg/m^2)	17.6 ± 2.2	20.1 ± 1.4
vBMDtrab(mg/cm)	130.50 ± 29.64	127.81 ± 37.87
BMC (mg/mm)	74.78 ± 20.53	92.83 ± 12.79
Grip Force (N)	30.41 ± 5.59	31.07 ± 4.00
SD scores		
Height	-0.5 ± 1.0	-0.3 ± 0.9
Weight	-0.5 ± 0.4	-0.7 ± 0.6
BMI	-1.2 ± 1.0	-1.0 ± 0.8
vBMDtrab	-0.7 ± 0.8	-0.7 ± 0.8
BMC	-0.9 ± 0.8	-0.7 ± 0.8
Grip Force	0.0 ± 1.2	0.0 ± 1.0

The means in SD scores did not significantly differ between both groups ($p>0.2$ each).

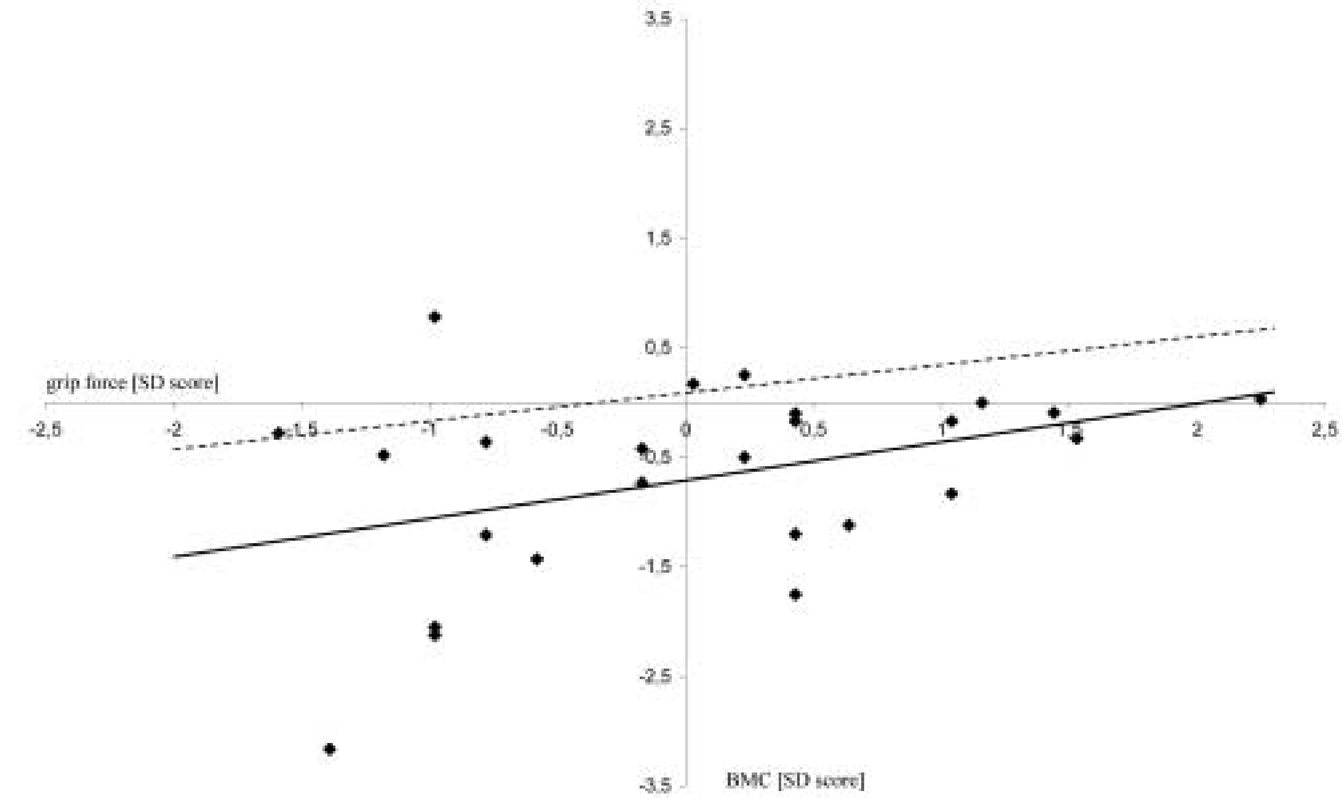

Figure 1. BMC is presented in relation to grip force in SD scores for the population of anorexic females. The linear regression line (BMC= 0.34 x grip force – 0.71) is drawn for the relationship between BMC and grip force as a black line. The constant is significantly different from the constant of the linear regression line of the reference group (DONALD Study, BMC= 0.44 x grip force + 0.02; painted as a black dotted line).

between 0° and 15° ulnar deviation. The subjects were told to put maximal force on the dynamometer. The maximal value of two trials was noted.

Psychiatric assessment

Psychiatric assessments were done by two trained psychiatrists following the same rules of assessment. Data about symptoms of eating disorders were evaluated by using the Eating Attitude Test 26 (EAT 26) and the Structured Interview for Anorexic and Bulimic disorders (SIAB) in the third revision[18]. According to these data the females were classified due to criteria of ICD-10[15].

Statistical analysis

Height, weight, BMI, BMC, vBMDtrab and grip force results were converted into age-specific SD scores using the formula: SD score = [(test result for a patient) – (age-specific mean in reference population)] / (age specific SD in reference population). Reference values for body height, body weight, BMI and vBMDtrab were used as recently published for the DONALD Study[14]. Reference values for BMC and grip force belong to the same population described above[14]. Means in SD scores were compared to reference population data by a one-sided Student's t-test (comparison of the mean of the SD score with zero). Means of sub-groups in the study group (still affected and recovered females) were also compared by two-tailed Student's t-test. Linear regression analysis was provided for the relationship between BMC and grip force in both groups. F-test was provided to test the regression models for significance (two-tailed). The constants and also regression co-efficients of the linear regression equations were compared with each other by the application of Student's t-tests following the description by Sachs[19]. A $p<0.05$ was assessed as significant for all provided tests. All these calculations were performed using standard software (SPSS software package, version 6.0 for Windows, SPSS, Inc, Chicago, IL).

Results

Anthropometric characteristics and results of musculoskeletal analyses in the entire study population are shown in SD scores in Table 1. In the following part, SD scores which are significantly different from zero indicate a signifi-

Table 3. Linear regression analyses for the relationship between BMC and grip force in SD scores.

Independent Variable	r^2		SE of the Estimate		Regression Co-efficient		Constant		p (F)	
	S	R	S	R	S	R	S	R	S	R
Grip Force	0.39	0.44	0.83	0.89	0.34	0.44	-0.71	0.02	0.05	<0.05

Abbreviations: S= study group (N = 25), R= reference group (DONALD Study), N= 271

cant difference in comparison to the reference population. The SD score for mean height was normal, but the means of SD scores of body weight and BMI were significantly decreased. The mean SD scores of BMC and vBMDtrab were also significantly decreased, whereas the SD score for the mean grip force was in the normal range. Mean BMC SD score was significantly lower than mean grip force SD score in the study group ($p<0.05$; paired and two-tailed Student's t-test). The mean for the SD score of vBMDtrab was not significantly different from the mean BMC SD score in the study group ($p>0.2$; paired and two-tailed t-test).

When patients who are still affected by eating disorders were separated from recovered females in the study group (shown in SD scores for height, weight, BMI, BMC, vBMDtrab and grip force in Table 2), the means in SD scores were not different between the two sub-groups for any parameter ($p>0.2$ each; two-tailed Student's t-test). Concerning EE the mean of the cumulative dose of EE was not different between the two sub-groups ($p=0.19$, two-tailed Student's t-test).

The calculated linear regression equations for the relationship between BMC and muscle force are presented in Table 3 and visualized in Figure 1. The statistical comparison of the constants for the regression equations revealed a significantly lower constant in the study than in the control group ($p<0.05$, two-tailed Student's t-test), whereas the regression co-efficient was not significantly lower in the study group than in the control group ($p>0.2$, two-tailed Student's t-test).

Discussion

Auxologic parameters, grip force and BMC were normalized to age delivering SD scores in the first step of analysis. The means of these SD scores were compared to the reference group by a comparison of SD scores with zero. These parameters were also compared with each other for the entire study group. Females of the study group had lower values for BMI and BMC, but similar values of grip force in comparison to females of the reference group. The comparison of these parameters revealed a lower mean BMC SD score than mean grip force SD score in the study group. This result leads to the suggestion that the adaptation of bone mass to grip force is disturbed in individuals with a permanent or former episode of AN.

The parameters of the linear regression equations were compared between the study group and the reference population in order to investigate the relationship between BMC and grip force in more detail (Table 3). A difference between constants indicated a difference in set points of the cybernetic system. Thereby, a lower set point is expressed by a lower constant. Thus, females with a lower set point possess less bone mass at the same level of muscle force. We have yet previously described this phenomenon in female adolescents in relation to their pubertal status[14]. In puberty females possess more bone mass in relation to muscle force than females before entering puberty[20]. It can be suggested that a higher set point is associated with the presence of higher estrogen levels, whereas a lower set point could indicate a decreased level of estrogens according to ovarian dysfunction. In our analysis, the comparison of the constants of the linear regression equations indicated a significantly lower set point in the study group, which is likely one of the reasons for a decreased BMC in AN.

The data of this study were also compared with already published data on osteoporosis in AN. Thereby, the data of our study were compared with the published data of Resch et al. by the use of two-tailed Student's t-tests[21]. The BMC SD scores of our present study were not significantly different from BMC SD scores measured in 20 anorexic females by Resch et al. ($p>0.2$).

The recently published study by Karlsson et al.[7] investigates the effect of ERT on bone mass and bone density of the vertebra and the femoral neck in AN. Their results also indicate that females with a former episode of AN have a reduced vBMD, if they were not treated with ERT. Therefore, Karlsson et al. support the concept that estrogens facilitate the acquisition of bone mass, which might be explained by the increase of the set point due to estrogens.

Moreover, Bachrach et al. showed an increase in BMD after recovery from AN in a follow-up study design[22]. When our study group was separated into recovered and still affected females, a significant difference of mean BMC SD scores was not detected between these two groups. An explanation might be that recovered females also had significantly lower BMI than females of the DONALD Study reference population. This result can lead to the suggestion that permanently spontaneous relapses and also spontaneous remissions appeared in our study group. Those permanent transitions are in concordance with the literature reporting relapses and transition between sub-types of AN as a common phenomenon in AN[2]. Thereby, transiently relapsing individuals do not have a permanent ovarian function and present a bias in the classification of recovered and still affected females in a cross-sectional study design. Therefore, a recent recovery from AN should not mention a permanent recovery in ovarian function in a cross-sectional study.

The cumulative dose of EE was not significantly different between recovered and still affected individuals in our study group. This might also be explained by the transition of individuals between these both groups as it has been described in the paragraph above. Because estrogen levels were not monitored over the time in our study design, a connection between current or previous estrogen levels and the set point of mechanical stability of the bone could not be investigated. But this is an interesting issue which could test the pharmacological concept of ERT in a longitudinal study design.

In conclusion, the manifestation of AN during the time of puberty decreases bone mass even years after the primary episode of AN. The constant of the linear regression model for the relationship between muscle force and bone mass was significantly lower in the study group than in the reference group Therefore, the formulated hypothesis of the introduction can be rejected. This result indicates that females with a present or former episode of AN have a lower set point for the acquisition of bone mass due to mechanical stimuli than unaffected females. Moreover, we could show in this study that the musculoskeletal analysis might deliver additional information about the cybernetic aspects of the pathogenesis of osteoporosis in females with AN, which finally contributes to a more sophisticated point of view on the pathogenetic aspects of osteoporosis in AN.

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