Evidence of a link between resting energy expenditure and bone remodelling, glucose homeostasis and adipokine variations in adolescent girls with anorexia nervosa

Laurent Maïmoun[1,2], Sébastien Guillaume[3], Patrick Lefebvre[4], Pascal Philibert[5], Helena Bertet[6], Marie-Christine Picot[6,7], Laura Gaspari[8], Françoise Paris[5,9], Maude Seneque[3], Anne-Marie Dupuys[5], Philippe Courtet[3], Eric Thomas[10], Denis Mariano-Goulart[1,2], Jacques Bringer[4], Eric Renard[4,7,11] and Charles Sultan[9]

[1]Service de Médecine Nucléaire, Hôpital Lapeyronie, Centre Hospitalier Régional Universitaire (CHRU) Montpellier et Université Montpellier 1 (UMI), 34295 Montpellier, France.
[2]Physiologie et Médecine Expérimentale du Cœur et des Muscles (PhyMedExp), University of Montpellier, INSERM U1046, CNRS UMR 9214. 34295 Montpellier cedex 5. Montpellier, France.
[3]Département d'Urgence et Post-Urgence Psychiatrique, Hôpital Lapeyronie, CHRU Montpellier, UMI, INSERM U1061, 34295 Montpellier, France.
[4]Departement of Endocrinology, Diabetes, Nutrition, Hôpital Lapeyronie, CHRU Montpellier, 34295 Montpellier, France.
[5]Departement de Biochimie et d'Hormonologie, Hôpital Lapeyronie, CHRU Montpellier, 34295 Montpellier, France.
[6]Unité de Recherche Clinique et Epidémiologie, Hôpital Lapeyronie, CHRU Montpellier, 34295 Montpellier, France.
[7]CIC INSERM 1411, Hôpital Saint Eloi, CHRU Montpellier, 34295 Montpellier cedex 5, France.
[8]Département de Pédiatrie, Hôpital Caremeau, CHRU Nîmes, 30000 Nîmes, France.
[9]Unité d'Endocrinologie et Gynécologie Pédiatrique, Département de Pédiatrie, Hôpital Arnaud de Villeneuve, CHRU Montpellier et UMI, 34295 Montpellier, France.
[10]Service de Rhumatologie, Hôpital Lapeyronie, CHRU Montpellier, 34295 Montpellier, France.
[11] Institut de Génomique Fonctionnelle, CNRS UMR 5203/INSERM U1161/Université Montpellier, Montpellier, France.

ABSTRACT

Purpose: Low areal bone mineral density (aBMD) is a well-known consequence of anorexia nervosa (AN). However, the impact of reduced energy expenditure on bone metabolism is unknown. This study assessed the effects of energy deficiency on bone remodelling and its potential interactions with glucose homeostasis and adipose tissue-derived hormones in AN, a clinical model for reduced energy expenditure.

Methods: Fifty women with AN and 50 age-matched controls (mean age 18.1±2.7 and 18.0±2.1 yrs, respectively) were enrolled. aBMD was determined with DXA. Resting energy expenditure (REEm), a marker of energy status, was indirectly assessed by calorimetry. Bone turnover markers, undercarboxylated osteocalcin (ucOC), parameters of glucose homeostasis, adipokines and growth factors were concomitantly evaluated.

Results: AN patients presented low aBMD at all bone sites. REEm, bone formation markers, ucOC, glucose, insulin, HOMA-IR, leptin and IGF-1 were significantly reduced, whereas the bone resorption marker, leptin receptor (sOB-R), and adiponectin were elevated in AN compared with CON. In AN patients, REEm was positively correlated with weight, BMI, whole body (WB) fat mass, WB fat-free soft tissue, markers of bone formation, glucose, insulin, HOMA-IR, leptin, and IGF-1, and negatively correlated with the bone resorption marker and sOB-R. Biological parameters, aBMD excepted, appeared more affected by the weight variation in the last 6 months than by the disease duration.

Conclusions: The strong interrelationships between REEm and bone remodelling, glucose homeostasis and adipokines underscore the importance of preventing energy deficiency to limit short- and long-term bone demineralisation and hormonal alterations in AN patients.

INTRODUCTION

A recent hypothesis suggested that bone remodelling is energetically costly for the rest of the body and may therefore be affected by the energy disposal of the organism [1]. The hypothesised link between energy status and bone remodelling in humans is further supported by the observations of low bone mass acquisition in patients with anorexia nervosa (AN) [2], and the increased bone mass in young obese individuals [3]. Moreover, based on experimental studies, bone is now considered to be an endocrine organ that contributes to the regulation of glucose metabolism and energy expenditure [4]. Murine knockout models (Ocn-/-) have clearly shown that osteocalcin (OC), a protein specifically secreted by osteoblasts, is involved in this process [4]

AIM

The aim of the study was to investigate the relationship between energy metabolism measured by calorimetry and bone status in a condition of dramatic undernutrition in adolescents and young women with AN. Moreover, the potential interactions between energy status, bone metabolism, glucose homeostasis and adipose tissue-derived hormones were concomitantly evaluated

PATIENTS AND METHODS

A total of 100 adolescent and young women with ages ranging from 14.4 to 23.8 years (mean 18.1 ± 2.3) were enrolled in this study. Fifty of them had been diagnosed with anorexia nervosa. Patients were consecutively recruited from the Endocrinology Department at Montpellier University Hospital (France) in 2009-2012. They fulfilled the criteria for the diagnosis of AN as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV, i.e. amenorrhoea, body mass index (BMI) <18 kg/m², fear of gaining weight and alteration in body size perception (American Psychiatric Association, 1994). The aBMD was determined using dual-X-ray absorptiometry (Hologic QDR-4500A, Hologic, Inc., Waltham, MA) at whole body (WB), total proximal femur (TPF), lumbar spine (LS) and Radius. Measured REE (REEm) was assessed over a period of at least 30 min by indirect calorimetry (Quark RMR, Cosmed, Rome, Italy) after an overnight fast in the patients with AN.

RESULTS

aBMD at all bone sites was significantly lower in patients with AN compared with CON (whole body [-4.7%], lumbar spine [-14.8%], hip [-15.6%], FN [-14.9%] and radius [-4.6%]). Concerning biological parameters, markers of bone formation [osteocalcin (OC) and PINP], leptin, free leptin index (FLI) , ucOC, glucose, insulin, HOMA-IR, IGF-1, and IGF-1/IGFBP-3 were significantly lower in AN whereas marker of bone resorption CTX), sOB-R and adiponectin levels were significantly higher. The values of REEm (992.3 ± 154.8) indicated hypometabolism in AN.

REEm in the AN patients was significantly and positively correlated with weight, BMI, WB FM, WB FFST, PINP, OC, glucose, insulin, HOMA-IR, leptin, FLI, IGF-1 and IGFBP-3, and negatively with CTX and sOB-R. In the multivariate model, increases in WB FFST ($p<0.01$), PINP ($p<0.01$), and HOMA IR ($p<0.01$) and a decrease in CTX ($p<0.001$) were associated with an increase of REEm. These variables explained respectively 14%, 13%, 19% and 21% of the REEm variance, with a total explained variance of 67%.

No correlation was found between the duration of the disease and REEm, bone parameters, glucose metabolism or anthropometric factors. A negative correlation was found only between the duration of AN and aBMD at hip ($r=-0.39$; $p<0.01$) and the CTX level ($r=-0.3$, $p=0.03$

Table 1. Main anthropometric and biological data in patients with anorexia nervosa and in controles

Parameters	Controls (n=50)	Patients with AN (n=50)	Difference, %[a]	p-value
Age, yr	18.1 ± 2.7	18.0 ± 2.1		0.69
Duration of AN, yr		2.1 ± 1.8		
Weight, kg	58.8 ± 8.1	42.2 ± 5.4		**<0.001**
Whole body fat mass, %	24.5 ± 5.6	15.9 ± 5.6		**<0.001**
Areal Bone Mineral Density (g.cm^{-2})				
Whole body	1.076 ± 0.075	1.025 ± 0.089	-4.7	**<0.01**
Lumbar spine	0.990 ± 0.115	0.843 ± 0.101	-14.8	**<0.001**
Hip	0.965 ± 0.103	0.813 ± 0.123	-15.6	**<0.001**
FN	0.876 ± 0.102	0.745 ± 0.118	-14.9	**<0.001**
Radius	0.542 ± 0.031	0.517 ± 0.045	-4.6	**<0.01**
Biological Parameters				
CTX, ng/ml	0.580 ± 0.210	0.895 ± 0.365	+55.2	**<0.001**
PINP, ng/ml	108.9 ± 83.9	60.2 ± 35.6	-44.8	**<0.001**
OC, ng/ml	39.0 ± 20.1	24.5 ± 10.5	-37.2	**<0.001**
ucOC, ng/ml	6.2 ± 3.7	2.4 ± 2.6	-61.3	**<0.001**
Glucose, mmol/l	4.69 ± 0.55	4.16 ± 0.79	-11.3	**<0.001**
Insulin, µU/ml	10.7 ± 3.7	4.8 ± 3.3	-55.1	**<0.001**
HOMA-IR	2.24 ± 0.88	0.92 ± 0.70	-59.1	**<0.001**
Leptin, ng/ml	9.61 ± 5.95	1.27 ± 1.47	-86.8	**<0.001**
sOB-R, ng/ml	24.0 ± 8.5	39.6 ± 12.1	+65.0	**<0.001**
FLI	0.51 ± 0.48	0.04 ± 0.05	-92.2	**<0.001**
Adiponectin, µg/ml	12.0 ± 5.8	19.0 ± 7.7	+58.3	**<0.001**
IGF-1, ng/ml	317.0 ± 109.3	183.8 ± 76.1	-42.0	**<0.001**
IGFBP-3, ng/ml	5420.7 ± 1094.1	5005.7 ± 1178.8	-7.7	0.07
IGF-1/IGFBP-3 ratio	5.9 ± 1.9	3.6 ± 1.1	-39.0	**<0.001**
Energy metabolism				
REE_m, kcal/d	-	992.3 ± 154.8	-	-
REEp, kcal/d	1432.5 ± 83.7	1276.8 ± 57.2	-10.9	**<0.001**
Predicted REE values, %	-	-22.4 ± 10.7	-	-

Values are presented as mean ± SD. Resting energy expenditure predicted (REEp),

Table 2. Correlation analysis between REEm and REEp and different parameters in patients with AN and CON.

Parameters	Patients with AN REE_m	Patients with AN REE_p	Controls REE_p
Weight, kg	0.59***	a	a
BMI, kg/m²	0.64***	a	a
Duration of AN, yr	0.21	0.07	-
Amenorrhoea duration, mo	-0.004	-0.03	-
WB aBMD, g.cm²	-0.01	0.33*	0.22
L1-L4 aBMD, g.cm²	-0.03	0.37**	0.38**
hip aBMD, g.cm²	-0.01	0.28*	0.19
FN aBMD, g.cm²	-0.07	0.55**	0.15
Radius aBMD, g.cm²	-0.04	0.09	0.16
WB FM, kg	0.51***	0.61***	0.88***
WB FFST, kg	0.45**	0.86***	0.83***
CTX, ng/ml	-0.46***	-0.22	-0.06
PINP, ng/ml	0.50***	0.24	-0.13
OC, ng/ml	0.47***	0.30*	-0.21*
ucOC, ng/ml	0.24	0.18	-0.05
Glucose, mmol/l	0.36*	0.29*	0.21
Insulin, µU/ml	0.46***	0.24	0.09
HOMA-IR	0.52***	0.34*	0.11
Leptin, ng/ml	0.57***	0.46**	0.56***
sOB-R, ng/ml	-0.29*	-0.38**	-0.25(p=0.09)
FLI	0.59***	0.49***	0.52***
Adiponectin, µg/ml	0.04	-0.10	-0.27
IGF-1, ng/ml	0.63***	0.54***	0.22
IGFBP-3, ng/ml	0.45**	0.57***	0.18

* for $p<0.05$, ** $p<0.01$ and *** $p<0.001$

CONCLUSION

The strong interrelationships between REEm and bone remodelling, glucose homeostasis and adipokines underscore the importance of preventing energy deficiency to limit short- and long-term bone demineralisation and hormonal alterations in AN patients.

*Corresponding author: ***Laurent Maïmoun:*** *Département de Médecine Nucléaire*, Hôpital Lapeyronie, CHRU de Montpellier, 191 avenue Doyen Gaston Giraud, 34295 Montpellier, Cedex 5, France, E-mail: l-maimoun@chu-montpellier.fr.

[1] Ferron M et Coll. (2014) Arch Biochem Biophys 561C: 137-146. [2] Maimoun L et Coll. (2014) J Clin Endocrinol Metab **99: E582-90. [3] Leonard MB et Coll. (2004). [4] Am J Clin Nutr 80:514-523.**[5] Lee NK et Coll. (2007) Endocrine regulation of energy metabolism by the skeleton. Cell 130:456-469.

ESPE 2015 221-P2

Bone, Growth Plate and Mineral Metabolism

Mamoun laurent

DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology

PosterSessionOnline.com