Is serum serotonin involved in the bone loss of young females with anorexia nervosa ?

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ABSTRACT

Objective. Recent experimental data suggest that circulating serotonin interacts with bone metabolism, although this is less clear in humans. This study investigated whether serum serotonin interferes with bone metabolism in young women with anorexia nervosa (AN), a clinical model of energy deprivation.

Methods. Serum serotonin, markers of bone turnover [osteocalcin (OC), procollagen type I N-terminal propeptide (PINP), type I-C telopeptide breakdown products (CTX)], leptin, soluble leptin receptor (sOB-R), and insulin-like growth factor-1 (IGF-1) and its binding protein (IGFBP-3) were assessed. Whole body, spine, hip and radius areal bone mineral density BMD (aBMD) were assessed by dual-energy X-ray absorptiometry in 21 patients with AN and 19 age-matched controls.

Results. Serum serotonin, leptin, IGF-1, IGFBP-3, OC, PINP and aBMD at all sites, radius excepted, were significantly reduced in AN whereas CTX and sOB-R were increased compared with controls. Serum serotonin levels were positively correlated with weight, body mass index, whole body fat mass, leptin and IGF-1, and negatively with CTX for the entire population.

Conclusions. Low serum serotonin levels are observed in patients with AN. Although no direct link between low serum serotonin levels and bone mass was identified in these patients, the negative relationship between serotonin and markers of bone resorption found in all population nevertheless suggests the implication of serotonin in bone metabolism. Impact of low serum serotonin on bone in AN warrants further studies.

INTRODUCTION

Low bone mass is a major complication of anorexia nervosa (AN) [1]. Among hormonal factors, an alteration in circulating estradiol, IGF-1, and cortisol may be implicated in this bone demineralisation [2]. Based on new findings, it was demonstrated a neuro-skeletal pathways [3]. Then, leptin inhibits bone mass accrual by inhibiting serotonin synthesis and/or release by brainstem neurons. Brain serotonin favors bone mass accrual by acting through a serotonin receptor, Htr2c, which is expressed by ventromedial hypothalamus neurons that act from the sympathetic nervous system through the β2 adrenergic receptor expressed in osteoblasts. However, serotonin presents bimodal osteotropic effects, since the serotonin released from the duodenum inhibits osteoblast activity and thereby decreases bone formation [4]. The studies that directly address the skeletal effect of circulating serotonin in women are rare and no study has yet evaluated this effect in AN, a clinical model of energy deprivation. Given the well known deleterious effects of nutritional deprivation on bone mass and more specifically the negative action of decrease tryptophan [5], a precursor of serotonin, low levels of plasma serotonin may be involved in the pathophysiology of bone loss in AN.

AIM

The aim of this study was to investigate the potential involvement of serum serotonin in the early and severe bone loss of young females with AN.

PATIENTS AND METHODS

Forty adolescent and young women were enrolled in this study. Twenty-one of them had been diagnosed with anorexia nervosa. They fulfilled the criteria for the diagnosis of restrictive AN as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV: amenorrhea, body mass index (BMI) <18 kg/m², fear of gaining weight, and alteration in body size perception (American Psychiatric Association, 1994). The control group (CON) was recruited from the community by advertisement. It consisted of 19 healthy normal-weight women with 18<BMI<25 kg/m². 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. Osteocalcin (OC), procollagen type I N-terminal propeptide (PINP), type I-C telopeptide breakdown products (CTX) were leptin, soluble leptin receptor (sOB-R), IGF-1 and serotonin were assayed.

RESULTS

Except for the radius, aBMD at all bone sites was significantly lower in patients with AN compared with CON [whole body (-5%), lumbar spine (-18%), and hip (-14%)] **(Table 1)**.

Regarding bone remodeling, patients with AN presented lower values for markers of bone formation (OC and PINP; p<0.001) and a higher mean value for the bone resorption marker (CTX; p<0.01). Fasting serum leptin, FLI, serotonin and IGF-1 were significantly and severely decreased (all at p<0.01) in patients with AN, whereas fasting serum sOB-R was significantly higher (p<0.001) **(Table 1).**

When the data from AN patients and controls were pooled, the serotonin level was positively correlated with weight, IMC, WB-FM, leptin, FLI and IGF-1 and negatively correlated with CTX **(Table 2).** These correlations disappeared when only AN patients were studied. In controls, the serum serotonin levels were negatively correlated with BMI, WB-FFST and L1-L4 aBMD. As age may be considered as a confounding factor, the relationship between serotonin levels with BMD and bone markers was adjusted for age. No significant difference was observed before or after adjustment for age. No correlation between bone markers (PINP, OC) and serotonin or between aBMD at whole body, hip, radius and serotonin was observed whatever the group (whole population, AN and CON).

Table 1: Clinical and biological data of patients and controls.

Parameters	Controls	Patients with AN	Difference, %[a]	p-value
Number of subjects	n=19	n=21		
Age, yrs	18.9 2.8	18.3 2.1	-3	0.40
Weight, kg	58.8 8.4	40.8 5.2	-31	**<0.001**
Height, m	165.7 6.4	165.2 6.2	-0.3	0.81
BMI, kg/m²	21.4 2.1	15.0 1.9	-30	**<0.001**
WB-FM (%)	26.7 5.8	14.4 5.7	-46	**<0.001**
WB-FFST (kg)	40.6 4.2	33.1 3.8	-18	**<0.001**
aBone Mineral Density (g.cm-2)				
Whole body	1.098 0.086	1.043 0.086	-5	**0.05**
Lumbar spine	1.038 0.126	0.855 0.108	-18	**<0.001**
Hip	0.966 0.117	0.829 0.115	-14	**<0.001**
Radius	0.553 0.033	0.532 0.039	-4	0.09
Biological Parameters				
CTX, ng/ml	0.574 0.213	0.924 0.406	61	**<0.01**
PINP, ng/ml	96.6 51.7	52.0 35.0	-46	**<0.001**
OC, ng/ml	33.6 8.6	20.3 6.9	-40	**<0.001**
Leptin, ng/ml	10.2 6.3	1.1 1.1	-89	**<0.001**
sOB-R, ng/ml	17.8 5.9	39.8 15.8	124	**<0.001**
FLI	0.70 0.62	0.03 0.04	-96	**<0.001**
Serotonin, ng/ml	267.0 94.0	192.2 54.9	-28%	**0.002**
IGF-1, ng/ml	302.8 107.4	162.4 60.7	-46	**<0.001**

Values are presented as mean SD. aDifference = ((mean AN- mean CON)/meanCONT)*100. BMI: body mass index. WB: whole body, FM: fat mass, FFST: fat-free soft tissue, CTX: type I-C telopeptide breakdown products, PINP: procollagen type I N-terminal propeptide; OC: osteocalcin, sOB-R: soluble leptin receptor, FLI: free leptin index defined as leptin/sOB-R ratio, IGF-1: insulin-like growth factor-1.

Table 2. Correlation analysis between serum serotonin and anthropometric data, body composition and biological parameters.

Parameters	All population (n=40)	Patients with AN (n=21)	Controls (n=19)
Age, yr	0.15	0.07	0.13
Weight, kg	0.31*	0.02	-0.34
BMI, kg/m²	0.35*	0.14	-0.43*
WB-FFST, kg	0.24	-0.02	-0.46*
WB-FM, kg	0.38*	0.11	-0.11
aBMD whole body, g/cm²	0.08	0.14	-0.29
aBMD lumbar spine, g/cm²	0.28 (p=0.08)	0.28	-0.46*
aBMD hip, g/cm²	0.24	0.34	-0.31
aBMD, radius, g/cm²	-0.01	0.05	-0.35
CTX, ng/ml	-0.41**	-0.08	-0.37
PINP, ng/ml	0.15	-0.19	-0.18
OC, ng/ml	0.24	-0.05	-0.07
Leptin, ng/ml	0.40*	-0.004	-0.001
sOB-R, ng/ml	-0.28 (p=0.08)	-0.13	0.32
FLI	0.38*	0.03	-0.10
IGF-1, ng/ml	0.32*	0.31	-0.15

Data presented are Pearson or Spearman correlation coefficients according to the distribution of the variable.
* for p<0.05 and ** for p<0.01

CONCLUSION

Low serum serotonin levels are observed in patients with AN. Although we identified no direct link between these low serum serotonin levels and bone mass in this population, the negative relationship between serotonin and bone resorption markers suggests the implication of serotonin in bone metabolism. This warrants further studies in larger sample.

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