ASSESSMENT OF BONE METABOLISM IN OBESE WOMEN

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Objective. To evaluate the bone metabolism in obese women by the estimation of selected markers of bone formation.

Methods. The concentration of plasma parathyroid hormone (PTH) and selected markers of bone formation [osteocalcin (BGP) in plasma, carboxyterminal propeptide of type I procollagen (PICP) and alkaline phosphatase (AP) activity in blood serum] and bone resorption [cross-linked carboxyterminal telopeptide of type I collagen (ICTP) in blood serum and urinary excretion of calcium (Ca)] in 18 extremely obese women (BMI>40 kg/m²) with android phenotype (WHR>0.8) and in 20 healthy women with normal body weight. The age range of all subjects was 25 to 42 years (mean: 36.82 ± 3.95).

Results. All obese women showed significantly increased concentration of plasma PTH, BGP and serum PICP, ICTP and elevated urinary excretion of Ca.

Conclusion. The obtained results show that in extremely obese women with android phenotype bone metabolism disturbances may occur pointing at increased bone formation and resorption.

Key words: Bone Metabolism - Extremely Obese Women - Android Phenotype

Calcium and phosphorus metabolism and the related bone metabolism are regulated by many factors among which primary roles are played by parathyroid hormone (PTH), calcitonin (CT) and active metabolites of vitamin D. Their function consists of constantly controlling calcium absorption from the intestines as well as concentration of ionized calcium in the circulation and also bone remodeling (BODEN and KAPLAN 1990; MARTIN and MOSLEY 1990; DE LUCA 1992; RIZZOLI et al. 1992). Besides the calcitropic hormones, among important modulators of mineral and bone metabolism are also: growth hormone, insulin, thyroid, adrenal and gonadal hormones and probably melatonin (NISHIMURA 1990; ERNST and RODAN 1991; LISSOS et al. 1993). In obesity, especially in its extreme form, the disturbances of endocrine functioning are seen (GLASS 1989; BARANOWSKA 1995; OSTROWSKA et al. 1995, 1996ab, 1997a,b) which may have important impact on mineral and bone metabolism (NAGANT DE DEUXCHAINES and DEVOGELAER 1986; HAFFNER and BAUER 1992; CAULEY et al. 1994; SANDYK et al. 1995; OSTROWSKA et al. 1997c).

The aim of the present study was to evaluate the concentration of plasma parathyroid hormone (PTH) and selected markers of bone formation [osteocalcin (BGP) in plasma, carboxyterminal propeptide of type I procollagen (PICP), and alkaline phosphatase (AP) activity in serum] and bone resorption [cross-linked carboxyterminal telopeptide of type I collagen (ICTP) in serum and urinary excretion of calcium (Ca)] in extremely obese women with android phenotype.
Material and Methods

Eighteen obese women (BMI between 40.5 to 58 kg/m²) with android body fat distribution (WHR between 0.80 to 1.02) and regular menstrual cycles, aged 25 to 42 years were studied. A group of 20 age-matched clinically healthy women with normal body weight (BMI and WHR ranging 20 to 25 kg/m² and 0.72 to 0.76, respectively) served as controls. Additional data concerning age, clinical features and the values of BMI and WHR ratio of subjects studied are given in Tab. 1.

In all women the studies were performed in midfollicular phase on days 5 and 7 of the menstrual cycle. Fasting blood samples were taken between 8.30 and 9.00 in the Clinical Endocrinology Outpatient Department, Zabrze, in order to measure PTH levels and selected markers of bone metabolism [osteocalcin (BGP), carboxyterminal propeptide of type I procollagen (PICP), cross-linked carboxyterminal telopeptide of type I collagen (ICTP) and alkaline phosphatase activity (AP)]. Blood sampling for the measurements of PTH and BGP was collected using EDTA as an anticoagulant and blood sampling for the remaining measurements was collected without anticoagulant. Plasma and serum samples were obtained by centrifugation and stored at -70°C until assayed. Simultaneously, 24-hour urine was collected for calcium (Ca) measurements. Normality of the menstrual cycle was evaluated from the progesterone (P) levels on the 22nd day of the cycle.

Hormones and the majority of bone metabolism markers were measured using commercially available RIA kits: PTH (MEDGENIX, Belgium); BGP (ELSA-OSTEO-CIS bio international, France), PICP, ICTP, P (FARMOS, Finland). Serum AP level and urinary excretion of total calcium (Ca) measurements were determined using ALPHA DIAGNOSTICS kits (Poland).

The sensitivity of assays was as follows: PTH 1.8 pg/ml, BGP 0.4 ng/ml, PICP 1.2 µg/l, ICTP 0.34 µg/l, P 0.2 - 0.3 nmol/l. Linearity for AP and Ca methods were: 16 mg/dl and 1000 IU, respectively. The respective intraassay and interassay coefficients of variation were: PTH 2.4 and 6.8 %, BGP 3.9 and 4.9 %, PICP 3.1 and 5.8 %, ICTP 4.5 and 6 %, P 7.9 and 8.1 %, AP 7.8 and 8.5 %, Ca 4.7 and 6.8 %.

Results

Tab. 1 shows that obese women had significantly higher mean values of BMI (48.11 ± 7.90 kg/m²) and WHR (0.89 ± 0.07) when compared to these of controls (BMI 22.45 ± 2.08 kg/m²; WHR 0.74 ± 0.05).

Significantly increased mean level of plasma PTH, BGP, serum PICP, ICTP and urinary Ca excretion were demonstrated in all obese subjects vs. control group (Tab. 2). Mean values of alkaline phosphatase activity in serum were only slightly elevated compared to controls.

### Table 1

Subject characteristics and the values of body mass index (BMI) and waist to hip ratio (WHR) (range; mean ± SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25-41</td>
<td>25-42</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>36.51±4.42</td>
<td>35.83±3.82</td>
</tr>
<tr>
<td>Menstrual cycles</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Familial history of obesity</td>
<td>-</td>
<td>n=4(22.2%)</td>
</tr>
<tr>
<td>Body mass index (BMI-kg/m²)</td>
<td>20.25</td>
<td>40.5-58</td>
</tr>
<tr>
<td>Waist to hip ratio (WHR)</td>
<td>0.72-0.76</td>
<td>0.80-1.02</td>
</tr>
<tr>
<td></td>
<td>0.74±0.05</td>
<td>0.89±0.07</td>
</tr>
</tbody>
</table>

* - P ≤ 0.05 vs. control groups

### Table 2

Mean levels of parathyroid hormone (PTH) in plasma, osteocalcin (BGP), carboxyterminal propeptide of type I procollagen (PICP), cross-linked carboxyterminal telopeptide of type I collagen (ICTP) and alkaline phosphatase activity (AP) in obese women and in healthy volunteers

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control (n=20)</th>
<th>Obesity (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/ml)</td>
<td>19.45±2.98</td>
<td>31.08±3.09*</td>
</tr>
<tr>
<td>BGP (ng/ml)</td>
<td>18.71±3.92</td>
<td>34.14±3.80*</td>
</tr>
<tr>
<td>AP (U/l)</td>
<td>48.99±10.07</td>
<td>50.00±9.21</td>
</tr>
<tr>
<td>PICP (µg/l)</td>
<td>135.85±26.53</td>
<td>191.95±35.15*</td>
</tr>
<tr>
<td>ICTP (µg/l)</td>
<td>3.12±0.37</td>
<td>4.04±0.38*</td>
</tr>
<tr>
<td>Ca (mmol/24 h)</td>
<td>5.15±2.89</td>
<td>8.50±1.93*</td>
</tr>
</tbody>
</table>

* - P ≤ 0.05 vs. control group

The results are reported as mean±SD. Statistical evaluation of the results was performed using Student’s t-test for unpaired data.
Discussion

Only few authors estimated calcium and phosphorus metabolism and bone turnover in obesity. The measurements of PTH concentration in obese persons (which plays a crucial role in the regulation of mineral and bone metabolism) showed elevated values which depended on the degree of obesity (MOSEKILDE et al. 1980; BELL et al. 1985; ANDERSEN et al. 1986; GLASS 1989). We obtained similar results in all examined women having BMI above 40 kg/m² and WHR above 0.8. Increased PTH secretion may be explained by deficiency of active metabolites of vitamin D caused probably by a decreased exposition to sunlight (MOSEKILDE et al. 1980; COMPSTON et al. 1981; BELL et al. 1985; LIEL et al. 1988; GLASS 1989). COMPSTON et al. (1981) and LIEL et al. (1988) showed a characteristic decrease of average 25-OH-D₃ in obese patients who had BMI above 40 kg/m², as compared to persons with normal body mass. BELL et al. (1985) found in obese persons with increased PTH secretion a distinct decrease of 25-OH-D₃ which returns to normal values after the reduction of body mass. MOSEKILDE et al. (1980) observed in about 50 % of obese subjects treated by jejunoileostomy a persistent decrease in calcemia as well as concentration of 25-OH-D₃ and 1,25-(OH₂)-D₃ and in 18 % of patients increased values of PTH. It may be the result of increased risk of vitamin D poor absorption after jejunoileostomy whence the preventive use of vitamin D in obese subjects treated surgically (MOSEKILDE et al. 1980).

Other authors believe that increased PTH in obesity may result from changes in body localisation of particular forms of calcium leading to its increased excretion in urine (ANDERSEN et al. 1986).

In our previous studies with chosen markers of collagen synthesis and degradation (collagen makes up 90 % of total bone matrix) in obese women of reproductive age we found some changes pointing at elevated metabolism of this protein and which positively correlated with concentration of insulin, IGF-I and sex hormones while negatively with epinephrine, cortisol and thyroid hormones (OSTROWSKA et al. 1997 c). Female patients who showed body mass reduction (BMI lowered to less than 27 kg/m²) within 3 to 5 years following jejunoileostomy had normalized values of collagen biosynthesis markers [ie. terminal propeptides of type I procollagen (PICP) and type III procollagen (PIIINP)] as well as of the markers of this protein degradation (ie. hydroxyproline excreted in urine). The results of our studies point out to the influence of endocrine disturbances accompanying obesity (GLASS 1989; BARANOWSKA 1995; OSTROWSKA et al. 1995, 1996 a,b, 1997a,b) on the intensity of collagen metabolism.

In our current studies of women with extreme obesity and android phenotype we found significantly higher concentrations of BGP and PICP and slightly elevated activity of AP - a recognized marker of bone forming process (THOME et al. 1991). We also found considerably elevated values of ICTP and urine-excreted calcium - two reliable markers of bony tissue resorption (THOME et al. 1991). The results obtained suggest that there may be disturbances of bone metabolism accompanying obesity. They concern both increased bone formation and resorption. Such changes are most likely a consequence of endocrine disorders accompanying obesity.

Other authors estimated bone metabolism in obesity by using single or dual photon absorptiometry or (and) by determining concentration of urine-excreted hydroxyproline and calcium (KROLNER et al. 1982; JOHNSTON et al. 1985; DAVIE et al. 1986; RIBOT et al. 1988; HAFFNER and BAUER 1992). KROLNER et al. (1982) found in obese subjects of reproductive age treated surgically a decrease in density of minerals from spine which correlated positively with body mass changes. A positive association between bone density and obesity in untreated premenopausal women was also observed by HAFFNER and BAUER (1992). In obese patients undergoing therapy with low energy (2741-3301 KJ/day) and high calcium (28.9-35.1 mmol/day) diet DAVIE et al. (1986) noted that significantly more calcium was retained when dietary carbohydrate (CHO) intake was increased. However, urinary excretion of hydroxyproline increased with dieting, irrespective of dietary CHO. JOHNSTON et al. (1985) and RIBOT et al. (1988) found a decrease in bone density and increase in urine-excreted calcium in post-menopausal obese women. Such changes were less pronounced than these observed in healthy post-menopausal women. The authors suggest that increased weight on supporting bones in obese women may lead to an increase in anabolism hence the differences when such women are compared to controls (NAGANT DE DEUXCHAINES and DEVOGELAER 1986;
An important role can also be played by hyperestrogenism found in obese subjects (Nagant de Deuxchaines and Devogelaer 1986). Recently, the studies of melatonin effect on bone tissue (especially in post-menopausal women) suggest that this substance may be also an important modulator of bone restructuring (Sandyk et al. 1992). It is known that melatonin is an anti-aging hormone and that the menopause is associated with decline in melatonin secretion and increased rate of pineal calcification (Reitter 1991). Experimental data indicate that melatonin is involved in the regulation of calcium and phosphorus metabolism by stimulating PTH secretion and by inhibiting calcitonin release and prostaglandin synthesis (Martin and Mosley 1990; Rizzoli et al. 1992). In extreme obesity, especially of androidal type, a considerable increase of melatonin is observed (Ostrowska et al. 1995, 1996 a,b, 1997 b,c), which may also be the cause of minor disturbances of calcium-phosphorus metabolism and the related bone metabolism in post-menopausal obese women.

Based on the results of our studies as well as observations of other authors it may be inferred that changes of bone metabolism in obese women in reproductive age are a consequence of disturbances in secretion and action of such hormonal factors as: calcitropic hormones, IGF-I and its binding proteins, especially low-molecular-weight binding proteins as well as insulin and thyroid, adrenal and gonadal hormones and probably pineal melatonin (Glass 1989; Haffner and Bauer 1992; Cauley et al. 1994; Baranowska 1995; Sandyk et al. 1995; Ostrowska et al. 1995, 1996a,b, 1997a,b,c).

In summary, extreme obesity in women with androidal phenotype was shown to be accompanied by disturbances of bone tissue metabolism. They are expressed as changes due to increased bone formation and resorption which are caused, in all likelihood, by endocrine disturbances.

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