CALCIUM AND VITAMIN D STATUS IN MORBIDLY OBESE PATIENTS AND IN PATIENTS AFTER BILIOPANCREATIC DIVERSION/DUODENAL SWITCH

Natalya Mazurina*, Natalya Ogneva*, Ekaterina Troshina*, Yury Yashkov**, Alexander Ilyin*, Galina Melnichenko* and Ivan Dedov*

*Endocrinology Research Center, Moscow, Russian Federation., **The Center for Endosurgery and Lithotripsy, Moscow, Russian Federation.

ABSTRACT

Objective: The objective was to estimate the prevalence of inadequate vitamin D status and secondary hyperparathyroidism (SHPT) in morbidly obese patients and in patients who underwent biliopancreatic diversion/duodenal switch surgery (BPD/DS) Design: We compared 3 groups in the cross-sectional study: group 1 - morbidly obese (MO) patients with BMI > 40 and without type 2 diabetes mellitus (n=22), group 2 – patients in the long-term period after BPD/DS (n=23); group 3 – healthy normal weight controls (n=22). Results: 25(OH)D levels were significantly different in the controls (21.8 ng/ml), in the MO (8.8 ng/ml) and in the BPD/DS patients (8.6 ng/ml). Parathyroid hormone (PTH) elevation was found in 4 (18%) MO patients, in 12(52%) patients after BPD/DS, and was not detected in the control group. The frequency of SHPT was significantly higher in the operated group (52%) in comparison with the MO group (18%) (p=0.029). Conclusion: Vitamin D deficiency and secondary hyperparathyroidism are significantly more prevalent in MO patients than in normal weight subjects. In the long-term period after BPD, secondary hyperparathyroidism is more frequent than in MO and is not always accompanied by vitamin D depletion. Particular attention should be paid to adequate control of calcium metabolism and supplementation by calcium and vitamin D.

KEYWORDS: obesity, bariatric surgery, vitamin D, secondary hyperparathyroidism

Introduction

World Health Organization defines morbid obesity (MO) as BMI $\geq$ 40 kg/m$^2$ [1]. MO is associated with a pattern of serious diseases and may cause disability [2-4].

Links between hypovitaminosis D and obesity have been revealed in some population studies during the last ten years [5-8]. Now obesity is considered to be a risk factor for vitamin D deficiency and secondary hyperparathyroidism. Adiposity influences vitamin D status and morbidly obese patients have lower 25(OH)D concentrations.

Bariatric surgery has gained wide acceptance as a treatment of severe obesity, especially when complicated by type 2 diabetes mellitus, and results in the most significant and stable weight reduction in MO patients [9-11]. One of the most effective bariatric procedures is biliopancreatic diversion with duodenal switch (BPD/DS). BPD/DS is primarily malabsorptive and is a more complicated procedure than the Roux-en-Y gastric bypass. In this procedure a part of the lower stomach is removed. The part of the stomach that is left is connected directly to the last part of the small intestine (jejunum). Food completely bypasses a larger section of the small intestine than in the Roux-en-Y gastric

bypass. Consequently, digestion and absorption of macronutrients and micronutrients are primarily limited. Weight loss after BPD/DS lasts about 16-18 months postoperatively, with weight maintenance during the next period.

Malabsorption is a result of the anatomic changes imposed by bariatric surgery, and most of the patients are predisposed to calcium and vitamin D deficiency. Secondary hyperparathyroidism (SHPT) and osteoporosis may occur in the absence of adequate supplementation [12-15].

Among morbidly obese patients seeking bariatric surgery in the USA, vitamin D depletion was found in 60% cases, and an elevated PTH level was found in 48% cases [16]. Vitamin D insufficiency before the operation and alteration of micronutrient absorption after the operation may cause severe metabolic bone disease up to osteomalacia [17, 18].

The aim of the study:
To evaluate calcium and vitamin D status in morbidly obese patients and in patients who underwent BPD/DS.

Materials and methods:
A total of 67 patients 25-65-years-old of both genders were included in the cross-sectional study. Morbidly obese patients (n=22) were invited to the 1st group. Patients seeking weight reduction were recruited from Endocrinology Research Center outpatient clinic. Inclusion criteria were: BMI > 40, no significant body weight changes (over 3%) during the last year. Exclusion criteria were: type 2 diabetes mellitus diagnosed previously or at the moment of examination, weight loss therapy during the last year, polivitamin-mineral supplementation or calcium and vitamin D preparation intake during three months before the study enrollment.

Patients who underwent BPD with DS (Hess-Marceau modification) for morbid obesity in The Center for Endosurgery and Lithotripsy (n=23) were included in the 2nd group. The postoperative follow-up period was 2.3 to 7.2 years, median 4.7 years. BMI at the time of surgery was 50.8 [46.5; 60.8] and was matched to morbidly obese patients of the 1st group BMI. The length of the alimentary limb was 248.4 ± 9.4 cm, the length of the common channel 70.5 ± 2.3 cm. At the moment of the study 18 (78%) bariatric patients took vitamin and mineral supplementation. The daily dosage of elemental calcium varied from 1000 mg to 2000 mg, daily dosage of vitamin D was 800-1600 IU. Five patients of this group had no supplementation for micronutrient deficiency.

The control group was formed by healthy volunteers (n=22) with normal body weight (BMI 18.5-24.9). Subjects characteristics are shown in Table 1. Subjects of the three groups did not differ significantly in age and gender. The study was approved by Ethical Committee in Endocrinology Research Center, and all participants signed an informed consent before enrollment. The study was conducted in Moscow region. Blood samples for laboratory analysis were taken between October 2009 and April 2010 during the period of minimal exposure to sunlight.

Routine laboratory tests were performed for serum levels of total calcium (Ca), total protein, alkaline phosphatase (ALP), phosphorus (P), creatinine and urea with biochemical analyzer Hitachi 912 (Roche) in Clinical Biochemistry Department of Endocrinology Research Center.

The next formula was used to calculate serum ionized calcium (Ca ion):

\[
Ca^{+2} = \frac{24 \times Ca(\text{mmol/l}) + 0.33 \times total protein(\text{g/l})}{(0.1 \times total protein(\text{g/l}) + 6) \times 0.25}
\]

Chemiluminescence also analyzed serum for PTH level with analyzer Cobas 601 (Roche) and 25-hydroxyvitamin D (25(OH)D) level with analyzer “Liaison” (Tecan) in Biochemical Endocrinology and Hormone Research Department of Endocrinology Research Center. Vitamin D deficiency was defined as serum 25(OH)D level < 9 ng/ml, vitamin D insufficiency as 25(OH)D 9-29 ng/ml, and sufficiency as 30-100 ng/ml [19-24].

Data are presented as a median, 25th and 75th percentile. Kruskal-Wallis test was used to compare continuous data between groups. The χ² test and Fisher’s exact test were used to compare categorical data. Statistical significance was set at p<0.05. Statistical analyses were done in STATISTICA 6.0 (StatSoft® Inc., USA) for WINDOWS.

Results
Low serum Ca²⁺ level was found in 7 (32%) of MO patients. The same proportion of patients with hypocalcemia was observed in the controls (27%). In BPD/DS group serum Ca²⁺ level was low in 52% cases. Overall the difference in serum Ca²⁺ level between groups was not statistically significant (p=0.276). Vitamin D status in the MO patients and BPD/DS patients was strikingly different from the healthy control group (p<0.001). Compared with controls vitamin D deficiency (25(OH)D < 9 ng/ml) was more frequent in MO group (50% vs 9% cases) and in BPD/DS group (52% vs 9% cases). Only 5% of MO subjects and only 13% of operated patients had an optimal 25(OH)D serum concentration (30 ng/dl). In the control group, the rates of adequate vitamin D status were beyond the expected level – 23% only. (Fig.1)

![Fig 1. Vitamin D status in the MO patients and BPD/DS patients.](image)

The difference in PTH level between groups was also statistically significant (p<0.001). Elevated PTH was revealed in 4 (18%) MO patients and in 12 (52%) patient who underwent BPD/DS. Not a single case of serum PTH concentrations over the higher end of the normal range was found in the control group (Fig.2). All the patients with elevated PTH level had normal or decreased serum Ca and low vitamin D. These cases were considered to be secondary hyperparathyroidism. Prevalence of
Table 1 Characteristics of the patients. MO - morbid obesity; BPD/DS – biliopancreatic diversion/duodenal switch; BMI – body mass index, Q1 – 25th percentile, Q3 – 75th percentile.

<table>
<thead>
<tr>
<th></th>
<th>1st group (MO)</th>
<th>2nd group (BPD/DS)</th>
<th>3rd group (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>22</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Gender</td>
<td>Males - 6</td>
<td>Males - 6</td>
<td>Males - 6</td>
</tr>
<tr>
<td></td>
<td>Females - 16</td>
<td>Females - 17</td>
<td>Females - 16</td>
</tr>
<tr>
<td>Age (yr) (median, Q1, Q3)</td>
<td>44.5 [40; 50]</td>
<td>44.0 [40; 51]</td>
<td>44.0 [42; 51]</td>
</tr>
<tr>
<td>Waist circumference (cm)(median, Q1, Q3)</td>
<td>134.5 [120.0; 140.0]</td>
<td>106.0 [94.0; 122.0]</td>
<td>71.0 [68.0; 73.0]</td>
</tr>
</tbody>
</table>

Secondary hyperparathyroidism evaluated with Fisher’s exact test was maximal in BPD/DS group (p=0.029).

Results of laboratory testing are summarized in Table 2.

Discussion

Serum 25(OH)D concentration is the accepted biomarker for vitamin D status assessment. Seasonal variation must be taken into account while interpreting laboratory test results. In the present study, all blood samples were obtained during the winter season from October to April when exposure to the sunlight and skin’s vitamin D production are minimal. This could be the reason for low 25(OH)D level that has been found in the healthy controls. Our results confirm that obesity is associated with alterations in the vitamin D endocrine system and that 25(OH)D level is lower in morbidly obese individuals. Similar evidence was found in some previously published studies. In 2006 Carlin A. et al. demonstrated that 60% of morbidly obese patients seeking bariatric surgery had vitamin D deficiency [16]. Another cross-sectional study of vitamin D status in MO was published by Asheim E. et al. in 2008 [25]. If the reference interval commonly used for 25(OH)D had been applied, 55% of patients referred for weight-loss treatment from primary and secondary care in that study (BMI 45± 7 kg/m2) had inadequate vitamin D status.

The low levels of 25(OH)D in obesity are attributed to multiple factors. The first mechanism for vitamin D insufficiency is a direct consequence of obesity. After oral intake and absorption, vitamin D is sequestered and stored in fat tissue and then released slowly into the circulation. As in morbidly obese patients vitamin D is dissolved in the major fat depots, its bioavailability is decreased from dietary and cutaneous sources [26]. The second mechanism could be associated with decreased solar UV exposure and skin vitamin D synthesis because obese individuals may avoid it for social reasons.

The relation of body fat content and serum PTH has been investigated in population-based studies. A positive correlation between BMI and the level of PTH in plasma has been found [29, 30] According to previously published data, the prevalence of SHPT in MO patients is up to 50% [27, 28]. In some studies, the inverse relation between plasma PTH and 25(OH)D have been found, which suggests that the development of SHPT is a consequence of low vitamin D in the obese [31-33]. In our study, the prevalence of SHPT in MO group was 18%, and no significant inverse relation between PTH, 25(OH)D and BMI have been revealed. First of all, we must take into consideration a small number of included patients, so we cannot extend the results from this study to the population. On the other hand, there are some significant factors like age, sex, and duration of obesity that may explain variables of SHPT prevalence among the obese.

RYGBP is one of the most commonly performed bariatric procedures. That is why postoperative nutritional deficiencies were studied mostly in patients who underwent RYGBP. During the two years after RYGBP in spite of routine supplementation by standard multivitamin preparation, the incidence of specific nutrient deficiencies is reported to be up to 80% for vitamin B12, 60% for iron, 60-80% for calcium and vitamin D and 40 -45 % of folic acid [34]. In BPD with DS digestion and absorption are limited by “common channel” where biliopancreatic enzymes are mixed with food delivered by alimentary limb. BPD is associated with the most severe malabsorption. So all bariatric patients need additional nutritional assessment and additional prescriptions of appropriate doses of vitamins and minerals. Compliance of the patients who underwent BPS/DS is necessary regarding both taking vitamin-mineral supplementation and regular postoperative control with appropriate blood tests.

The decrease of vitamin D level and progressive increase of PTH are related to the length of bypass limb and the follow-up period after surgery. An inveres correlation has been estimated for vitamin D and PTH concentrations by Johnson J. et al. [35]. At the same time, not all patients whose vitamin D levels were lower than 30 ng/ml also had elevated PHT levels: only 49.0% of those who underwent short limb bypass and 78.9% of those...
Table 2 Comparison of biochemical testing results, 25(OH)D and PTH levels between groups. Kruskal-Wallis test. MO - morbid obesity; BPD/DS – biliopancreatic diversion/duodenal switch; Q1 – 25th percentile, Q3 – 75th percentile.

<table>
<thead>
<tr>
<th>Reference interval</th>
<th>1st group (MO)</th>
<th>2nd group (BPD)</th>
<th>3rd group (controls)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium (median, Q1, Q3) mmol/l</td>
<td>2.15-2.55 [2.27; 2.42]</td>
<td>2.16 [2.09; 2.30]</td>
<td>2.34 [2.30; 2.39]</td>
<td>P=0.276</td>
</tr>
<tr>
<td>Ionized calcium (median, Q1, Q3) mmol/l</td>
<td>1.03-1.29 [1.02; 1.08]</td>
<td>1.05 [0.97; 1.07]</td>
<td>1.06 [1.03; 1.09]</td>
<td>P=0.441</td>
</tr>
<tr>
<td>Phosphorus (median, Q1, Q3) mmol/l</td>
<td>0.87-1.45 [1.0; 1.3]</td>
<td>1.15 [1.1; 1.5]</td>
<td>1.2 [1.1; 1.3]</td>
<td>P=0.672</td>
</tr>
<tr>
<td>25(OH)D (median, Q1, Q3) ng/ml</td>
<td>30-80 [5.7; 13.0]</td>
<td>40.4 [56.7; 130.0]</td>
<td>88.0 [23.9; 42.3]</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>PTH (median, Q1, Q3) pg/ml</td>
<td>9.4-81.6 [33.7; 59.6]</td>
<td>40.4 [56.7; 130.0]</td>
<td>88.0 [23.9; 42.3]</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>ALP (median, Q1, Q3) mIU/l</td>
<td>62-106 [166.6; 222.0]</td>
<td>182.7 [100.0; 254.0]</td>
<td>169.0 [102.3; 137.0]</td>
<td>P=0.156</td>
</tr>
<tr>
<td>Total protein (median, Q1, Q3) g/l</td>
<td>60-87 [76.8; 81.6]</td>
<td>79.8 [69.1; 79.0]</td>
<td>75.0 [74.8; 81.2]</td>
<td>0.197</td>
</tr>
<tr>
<td>Creatinine (median, Q1, Q3) µmol/l</td>
<td>62-106 [62.4; 78.7]</td>
<td>70.5 [52.8; 70.3]</td>
<td>55.0 [59.4; 76.1]</td>
<td>P=0.863</td>
</tr>
</tbody>
</table>

who underwent long limb bypass [35]. It is interesting that 42.1% of the individuals with laboratory normal vitamin D levels had an elevation in PTH.

In the study published by Youssef Y. et al. [36], the frequency of SHPT 2 years after RYGBP was 53.3%. Vitamin D deficiency was present only in 30% of operated women diagnosed with SHPT. Perimenopausal age and African-American race were estimated as risk factors for SHPT development in women. In this study, 25(OH)D level was not associated with the length of bypass limb.

It is interesting that in morbidly obese patients there is a direct relationship between the level 25(OH)D and the level of PTH, but in patients who undergo bypass surgery, the correlation between 25(OH)D and PTH cannot be revealed [35-38]. When patients undergo GBP, the preferential sites for the absorption of calcium, the duodenum, and proximal jejunum are bypassed, so they have a risk of hypocalcaemia that only partially depends on vitamin D. In the study by Clements R. et al. patients were recruited one year after GBP: vitamin D deficiency was found in 23.6% cases, elevated PTH – in 25.7% cases [38]. Only 28.6% patients with SHPT had low 25(OH)D and in patients with vitamin D deficiency, only 36% had PTH elevation.

The results of our study have demonstrated a high prevalence of vitamin D deficiency in morbidly obese patients: only in 5% cases serum 25(OH)D level was adequate (≥ 30 ng/ml). Preoperative vitamin D nutritional status and PTH level should be evaluated in all patients who are seeking bariatric surgery. As morbidly obese patients have a higher incidence of SHPT than normal weight individuals, even before surgery, they need aggressive supplementation and regular biochemical monitoring to prevent the progression of calcium metabolism abnormalities and loss of bone mineral density. Our data underscore that standard polivitamin and mineral supplementation is not enough for impaired calcium absorption and SHPT correction in the long-term period after BPD/DS. Candidates for bariatric surgery should be informed about the importance of compliance with calcium and vitamin D supplementation. As malabsorption is an expected result of bypass surgery, the doses of calcium and vitamin D exceed those recommended for the treatment and prophylactic and should be defined individually. In the case of persistent abnormalities resistant for supplementation and additional treatment, reversal of BPD/DS with duodenal inclusion should be kept in mind and done before irreversible bone lesions are developed.

Fund
Supported by Russian Fundamental Research Found (grant number 11-04-00946 a).

Authors’ Statements
Competing Interests
The authors declare no conflict of interest.

References


