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Research Article

A Pilot Study on the Preoperative and Short-Term Postoperative Serum Fat-Soluble Vitamin Levels in Super-Obese Patients Undergoing a Biliopancreatic Diversion with Roux-En-Y Gastric Bypass (BPD/RYGBP) Malabsorptive Operation

Zoi Panagi[1,2]*, Panagiotis Bountouris[2], George Skroubis[3], Evangelia Papadimitriou[2], Maria Skouroliakou[4] and Fotis Kalfarentzos[3]

[1]*Department of Pharmacy, University Hospital of Patras, Rio, Patras, Greece*

[2]*Laboratory of Molecular Pharmacology, Department of Pharmacy, University of Patras, Rio, Patras, Greece*

[3]*Department of Surgery, School of Medicine, University of Patras, Rio, Greece*

[4]*Department of Dietetics and Nutritional Science, Harocopion University of Athens, Greece*

***Corresponding Author:** Zoi Panagi, Clinical Pharmacist, Department of Pharmacy, University Hospital of Patras, Rio, Patras, Greece.

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Abstract

Bariatric surgeries are considered the most effective approach to achieve weight loss in morbid obesity. Although their long-term weight loss results are remarkable, this is achieved at the expense of a considerably high rate of metabolic complications and post-operative nutrient deficiencies which require exogenous supplementation to maintain normal values in blood. Biliopancreatic Diversion with Roux-en-Y Gastric Bypass (BPD/RYGBP) is a particular type of BPD and has been effectively performed in super-obese patients in an attempt to achieve acceptable weight loss and resolution of co-morbidities without the high rate of metabolic complications reported for other types of biliopancreatic diversion. BPD/RYGBP manages loss by decreasing calorie uptake and promoting fat malabsorption. However, fat malabsorption may cause essential fat-soluble vitamin deficiencies which, if not treated properly, will result in severe clinical conditions. Although several metabolic deficiencies have been reported after RYGBP/PBD, the effect of this certain variant of BPD on fat-soluble vitamin levels in blood serum has not been studied. This study was therefore undertaken to investigate the effect of RYGBP/PBD operation on fat-soluble vitamin levels in patients' blood serum. The study population consisted of 15 super-obese (Body Mass Index > 50 kg/m^2) patients that have undergone BPD/RYGBP. Routine postoperative daily supplementation consisted of 1,200 μg vitamin A, 50 μg vitamin D_3, 10 mg vitamin E and 2,000 mg calcium. An HPLC method was developed in order to measure preoperative and short-term (1 year) postoperative serum levels of the fat-soluble vitamins A, D_3, 25(OH)D_3, E, E-acetate, δ-tocopherol and K2. Despite supplementation, the post-operative serum levels of all fat-soluble vitamins studied in patients that have undergone BPD/RYGBP operation progressively decreased. The decrease became statistically significant for vitamins D_3 ($p = 0.028$), 25(OH)D3 ($p = 0.026$), E ($p = 0.04$), δ-tocopherol ($p = 0.012$) and K_2 ($p = 0.005$) within the first year after surgery. The incidence of fat-soluble vitamin deficiencies found in our study was lower compared with other types of malabsorptive operations and indicates a possibility of fewer metabolic complications related to fat-soluble vitamin deficiencies. Although BPD/RYGBP operation seems to have decreased potential of metabolic complications, long-term postoperative monitoring of fat-soluble vitamin levels in serum is vital to determine individualized proper dosing for multivitamin supplement administration.

Keywords: *Morbid Obesity; Bariatric Operations; Fat-Soluble Vitamins; Serum Levels; Vitamins Deficiency*

Abbreviations

BPD: Biliopancreatic Diversion; RYGBP: Roux-en-Y Gastric Bypass; DS: Duodenal Switch; BPD/DS: Biliopancreatic Diversion with Duodenal Switch; BPD/RYGBP: Biliopancreatic Diversion with Roux-en-Y Gastric Bypass; PTH: Parathyroid Hormone; ALP: Alkaline Phosphatase; BMI: Body Mass Index

Introduction

Bariatric surgery seems to be the only effective approach for the long-term management of patients with morbid obesity [1]. Benefits of bariatric surgery include not only weight loss, but also, and probably more importantly, improvement in obesity-related co-morbidities [2].

Bariatric operations have been defined as restrictive, malabsorptive or combination of both [3]. Because of the high rate of weight loss failure observed with gastric restrictive operations, malabsorptive procedures are increasingly being performed all over the world. Biliopancreatic diversion (BPD), biliopancreatic diversion with duodenal switch (BPD/DS) and biliopancreatic diversion with Roux-en-Y gastric bypass (BPD/RYGBP) are surgical weight loss operations that induce weight loss by a combination of restriction and malabsorption. The initial weight loss is attributable to moderate gastric restriction. However, weight loss durability is thought to be due to malabsorption created by the diversion of pancreatic enzymes and bile from the alimentary tract and food bypassing the jejunum and proximal ileum [4]. The last 50-75 cm of distal ileum, also known as the common channel, is where the food is exposed to bile and pancreatic enzymes. This results in absorption of only 28% of ingested fat and 57% of ingested protein [5]. Although the long-term weight loss results are remarkable, this is achieved at the expense of a considerably high rate of metabolic complications [6-15]. Post-operative nutrient deficiencies are common and require exogenous supplementation to maintain normal values in blood [7,8,15]. Low levels of iron, vitamin B12, vitamin D and calcium are predominant after RYGBP [9, 11]. Protein and fat-soluble vitamins deficiencies are detected after all types of BPD studied so far [11-15].

Although metabolic abnormalities are expected after bariatric operations, they are frequently undiagnosed or misdiagnosed. Brolin and Leung noted a wide variation in the laboratory tests and the use of supplements following RYGBP or PBD in a survey of 109 bariatric surgeons [13]. While there is a lot of information on nutritional deficiencies after bariatric surgery for nutrients such as protein, iron, folic acid, calcium and water-soluble vitamins, there is not enough information for fat-soluble vitamins. This is attributed to the difficulty of fat-soluble vitamins isolation from the human blood, which is an expensive and time-consuming procedure. Most surgeons try to indirectly obtain information on the serum levels of fat-soluble vitamins by measuring the parathyroid hormone (PTH) serum levels, which are elevated in the case of D vitamin deficiency, or the prothrombin time, which is prolonged in the case of the K vitamin deficiency. In some cases, fat-soluble vitamins deficiencies were recognized from their clinical symptoms [16].

Super obesity (patients with Body Mass Index > 50 kg/m2) has a more complicated clinical course than morbid obesity, due to the increased incidence of co-morbidities. Thus, the primary goal of bariatric surgery in the super-obese patients should be the resolution or improvement of co-morbidities, rather than the achievement of normal body weight. A reduction of 10 - 20% of initial weight has been reported as sufficient for the resolution of co-morbidities [17].

Biliopancreatic diversion with Roux-en-Y gastric bypass reconstruction (BPD/RYGBP), as performed by F. Kalfarentzos and his colleagues, is a particular type of BPD and has been shown to be an effective and safe surgical procedure for the treatment of super-obese patients with pre-existing co-morbidities [18]. (BPD/RYGBP) is considered to achieve acceptable weight loss and resolution of co-morbidities without the high rate of metabolic complications reported for other types of biliopancreatic diversion. The initial weight loss of patients undergoing this variant of biliopancreatic diversion is related to the restriction of food intake, but the weight loss observed after the six first post-operative months and its maintenance seem to be due to the surgery-caused intestinal malabsorption of nutrients, especially of fat molecules and complex carbohydrates. As nutrient deficiencies are proportional to the length of absorptive area that is removed by surgery [4], a 100 cm common channel was surgically constructed [18] instead of the 50 - 75 cm common channel length observed in other types of BPD [13]. Although several metabolic deficiencies have been reported after (BPD/RYGBP) [11], the effect of this certain variant of BPD on post-operative fat-soluble vitamin levels in blood serum has not been studied. Therefore, the aim of the present work was to measure pre- and short-term (up to 1 year) post-operative levels of fat-soluble vitamins in patients that have undergone (BPD/RYGBP) and were receiving fat-soluble vitamin supplementation as mandatory post-operative care.

Methods

Patients

Study population consisted of 15 super-obese women (BMI > 50 kg/m^2 in association with up to five different co-morbitidies), who underwent BPD/RYGBP. All patients were evaluated preoperatively using a multidisciplinary approach, in order to optimize their preoperative physical condition. The patients' characteristics are shown in table 1.

		Range
Number of patients	15	
Sex	female	
Age (years)	40.2 ± 9.8	23 - 54
Height (cm)	161.3 ± 8.4	140 - 172
Weight (Kg)	151.9 ± 22.1	118.0 - 194.6
Excess weight (kg)	94.7 ± 18.6	73.0 - 131.3
BMI (kg/m^2)	58.2 ± 5.4	50.8 - 66.6
Co-morbidities	0 - 5/patient	

Table 1: *Pre-operative patient characteristics.*

Type of operation

The operation performed was BPD/RYGBP, a variant of the BPD surgical procedure. The main characteristics of BPD/RYGBP are: a gastric pouch of 30 ± 5 ml with complete separation from the bypassed stomach, a common limb of 100 cm, an alimentary limb almost always equal to 400 cm or smaller in the rare case of a lower than 500 cm small intestine's length, and as a biliopancreatic limb the remainder of the small intestine [18]. The main concern is to construct a total alimentary limb-alimentary plus common limb-at least 500 cm, based always in the total length of small intestine.

After surgery, all patients were prescribed the following fat- soluble vitamin supplements as mandatory post-operative care: 4,000 IU (1,200 μg) vitamin A, 2,000 IU (50 μg) vitamin D_3, 10 mg vitamin E and 2,000 mg calcium. An oral iron supplement was prescribed for all pre-menopausal women at a dose of 80 mg/day. Starting at 6 months post-operatively, vitamin B_{12} supplementation was given intramuscularly at a dose of 1,000 - 3,000 μg as necessary, depending on measured values. The patients were asked to undergo a series of serum laboratory tests. In addition to comprehensive electrolytes, hematology panel and iron levels, parathyroid hormone, alkaline phosphatase (ALP), calcium and fat-soluble vitamins (A, D_3, E, E-acetate, δ-tocopherol and K_2) were measured pre- and post-operatively at 1, 3, 6 and 12 months. The preoperative levels of fat-soluble vitamins determined for each patient, were used as control values with which all the post-operative fat-soluble vitamins levels were compared in order to assess the effect of RYGBP/PBD operation on fat-soluble vitamins levels.

HPLC determination of fat-soluble vitamins in patients serum

A Waters HPLC system consisting of a Waters 600 E system controller and a Waters 484 UV detector was used. The column was a Phenomenex Luna C18 (250 mm x 4,6 mm) 3 μm, operating at ambient temperature. The mobile phase consisted of a mixture of acetonitrile/methanol (CH_3CN-CH_3OH) delivered using a linear gradient, starting with a composition of 50 - 50% v/v and ending after 30 minutes at 70/30% v/v. A flow rate of 1.5 ml/min was used. Injection volume was 20 μl. Quantification was performed at 230 nm for DL-a-tocopherol (vitamin E), E-acetate, δ-tocopherol and D_3 (cholecalciferol), at 245 nm for menaquinone (K_2) and at 300 nm for retinol (vitamin A). The 25(OH)D_3 levels were calculated from corresponding D_3 values using the Binkley's equation [19]. Typical reference chromatograms of fat-soluble vitamins mixtures in pure methanol at 245 nm, 230 nm and 300 nm are presented in figure 1.

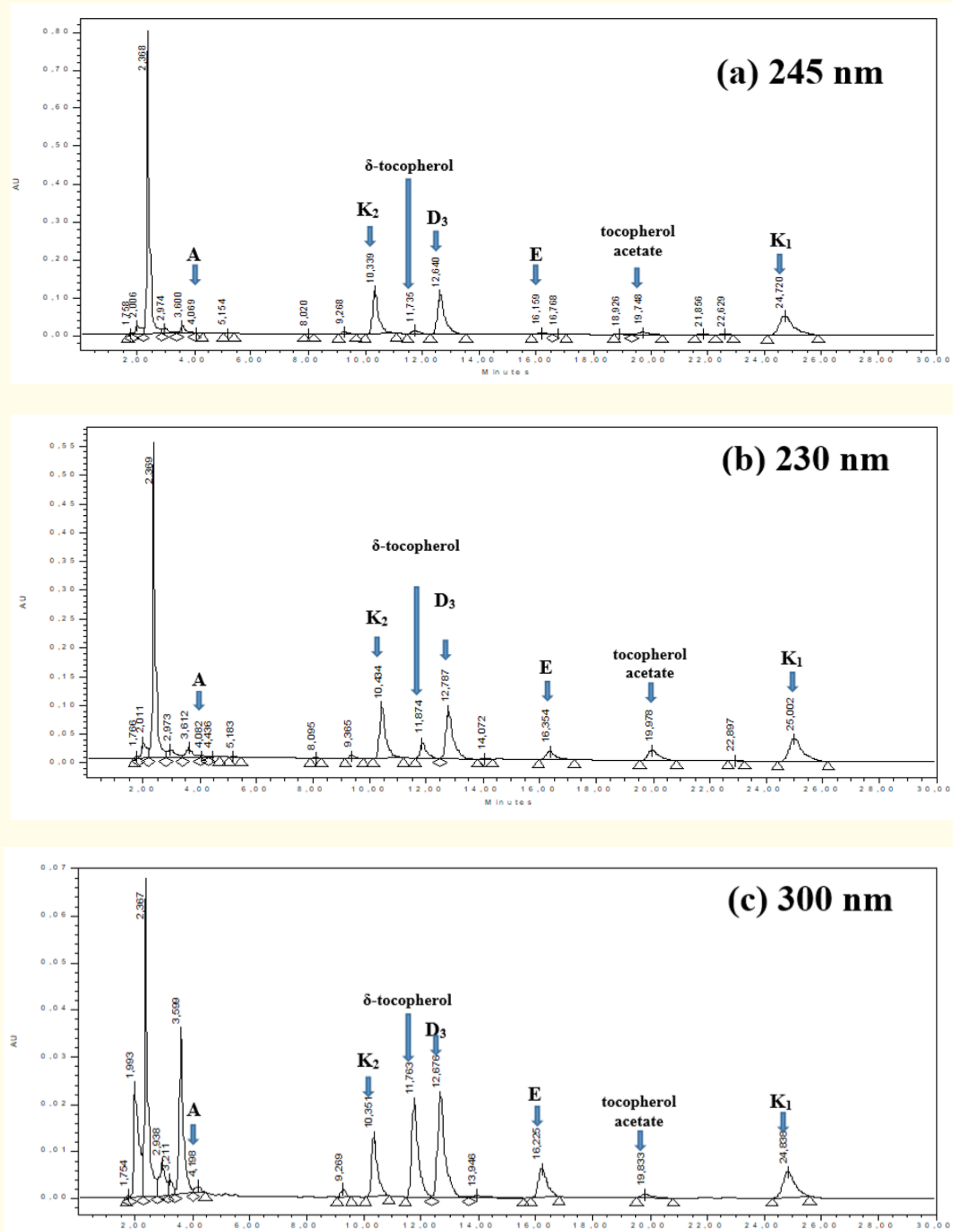
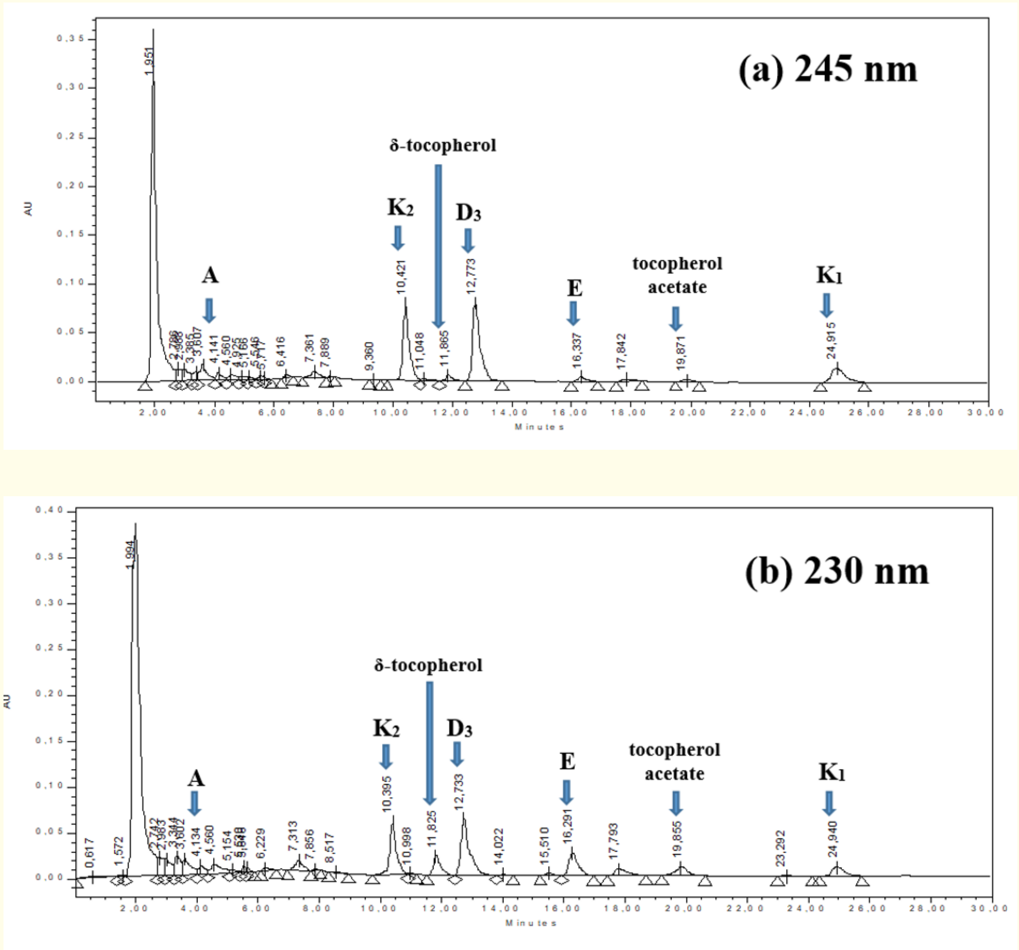


Figure 1: *Typical reference chromatograms of fat-soluble vitamins mixtures in pure methanol with no prior treatment at (a) 245 nm, (b) 230 nm and (c) 300 nm.*

A solid phase extraction procedure was used in order to isolate fat-soluble vitamins from patients' serum [20]. Aliquots of 1 ml human blood serum were treated with 5 ml of CH_3CN in order to precipitate proteins. After vortex mixing for 2 minutes, the sample was centrifuged at 25,000 x g at 4°C for 1h. The supernatant was subsequently applied to Bakerbond (SPE) Cyclohexyl (C_6H_{11}) 500 mg/3 ml cartridges, which had been conditioned immediately prior to use with 1 ml of methanol, followed by 1 ml of de-ionized water. The fat-soluble vitamins retained on the sorbent were eluted with 3 ml of methanol. The eluent was evaporated to dryness using a Speedvac evaporator and the dry residue of the fat-soluble vitamins' fraction was reconstituted in 100 μl of methanol, of which 20 μl were injected in the HPLC column. Identification was performed by UV spectra comparison using a Waters 484 UV detector. Recovery rates of fat-soluble vitamins from human blood serum exceeded 94% for all selected vitamins, which was considered quite satisfactory to proceed to the next stage of vitamin determination in unknown patient serum samples.

In figure 2, we present typical chromatograms of mixtures of fat-soluble vitamins at 245 nm, 230 nm and 300 nm, after mixing the mixture of vitamins with human blood serum and subsequent isolation according to the aforementioned protocol. These chromatograms demonstrate that the processing of serum samples with the method chosen does not influence the chromatographic behavior of fat soluble vitamins selected for this study. Fat-soluble retention times under the chromatographic conditions applied here are given in table 2.



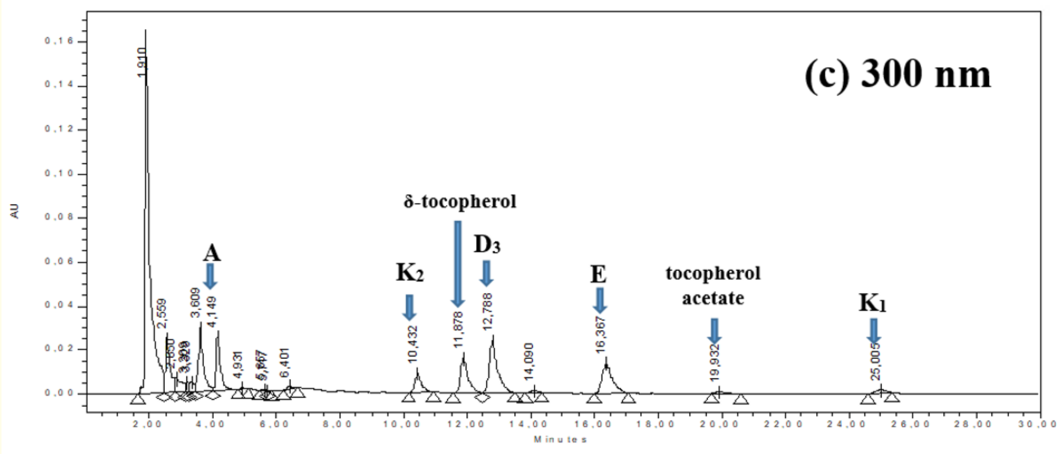


Figure 2: *Typical reference chromatograms of fat-soluble vitamins mixtures at (a) 245 nm, (b) 230 nm and (c) 300 nm, which have been subjected to the whole process of mixing with human blood serum and subsequent isolation according to the aforementioned protocol.*

Fat-soluble vitamins	Retention times
A	4,146 ± 0,065
K_2	10,417 ± 0,227
δ-tocopherol	11,805 ± 0,339
D_3	12,705 ± 0,370
DL-α-tocopherol **(E)**	16,292 ± 0,568
tocopherol-acetate	19,833 ± 0,630
K_1	24, 830 ± 0,891

Table 2: *Retention times of fat-soluble vitamins from the Phenomenex Luna column 3* **μm**, *C18 (2) (250 mm x 4.60 mm, 3* **μm**).

Statistical analysis

Statistical significance of the differences in the levels of each vitamin compared with the corresponding pre-operative levels was determined by ANOVA. Differences were considered as significant when $p < 0.05$.

Results and Discussion

The characteristics of the patients included in the present study are shown in table 1. Before operation, most of the patients had higher than normal serum levels of vitamins A, D_3, δ-tocopherol and K_2. The vitamin 25(OH)D_3 levels were within normal range whereas the levels of vitamin E were subnormal preoperatively. In all cases, as normal we considered the respective vitamin values of normal weight subjects. Although after surgery all patients were taking daily multivitamin supplements per os, the levels of all vitamins tended to decrease with time after BPD/RYGBP operation. One year after the bariatric operation, a significant decrease ($p < 0.05$) in D_3, 25(OH)D_3, E, δ-tocopherol and K_2 levels was observed compared to the preoperative levels, while the levels of vitamin A and E-acetate did not change significantly ($p > 0.05$) during the study period of one year (Figure 3).

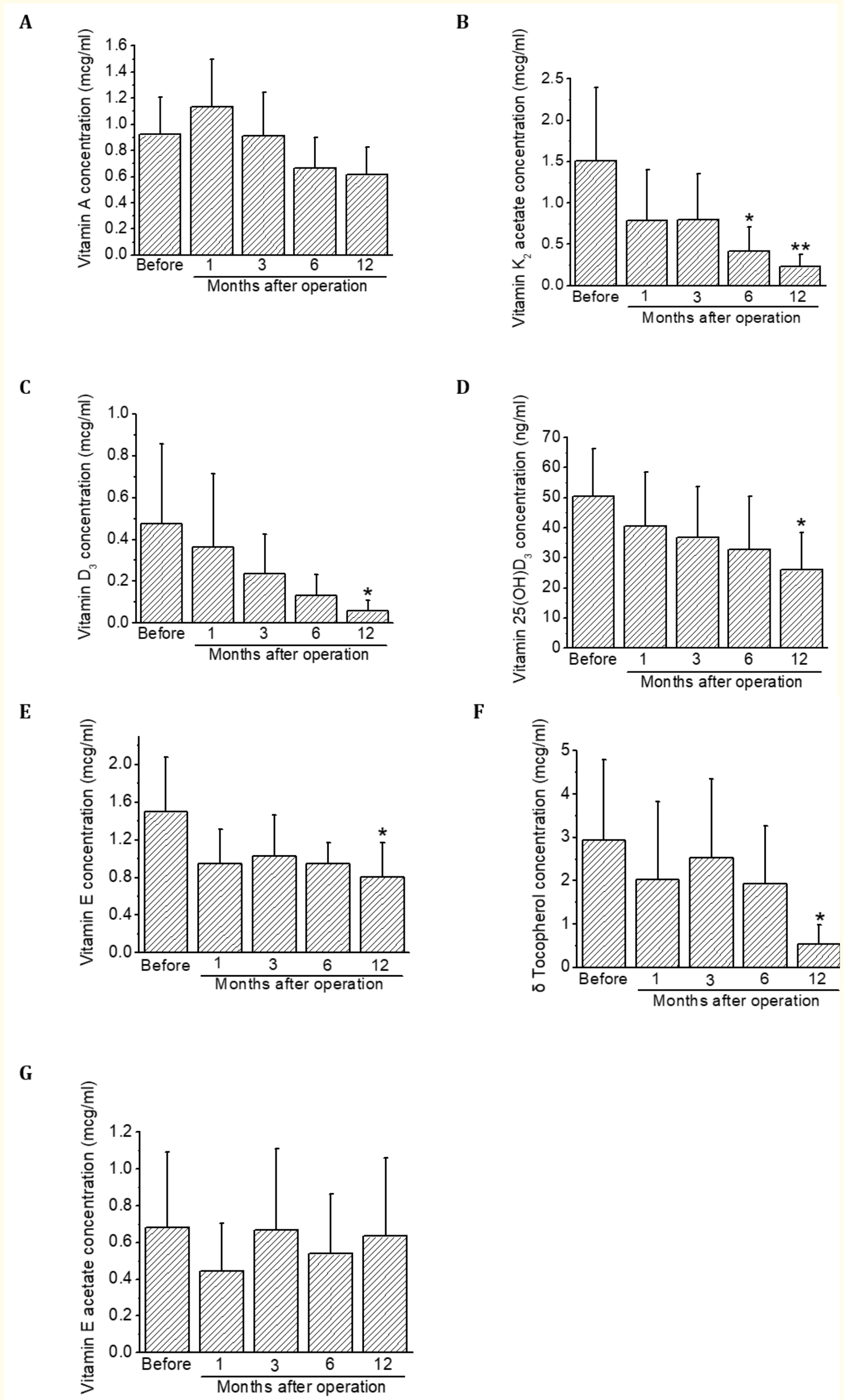


Figure 3: *Serum concentrations of fat-soluble vitamins at several time points after RYGBP/BPD bariatric surgery. Results are expressed as mean ± standard deviation of the amounts of each vitamin measured in patients' serum. Asterisks denote a statistical significance of the differences in the levels of each vitamin compared with the corresponding pre-operative levels (labeled as "Before"). *p < 0.05, **p < 0.01.*

The incidence of fat soluble vitamin deficiency pre-operatively was 13% for vitamin A, 20% for vitamin D_3, 20% for 25(OH)D_3, 40% for δ-tocopherol, 100% for vitamin E and 26.7% for vitamin K_2. One year after RYGBP/BPD surgery, the incidence of fat-soluble deficiency was measured to be 20% for vitamin A, 60% for vitamin D_3, 53% for 25(OH)D_3, 47% for δ-tocopherol, 100% for vitamin E and 53% for K_2. Based on the above, the incidence of fat soluble vitamin deficiencies that could be attributed to the RYGBP/BPD operation is shown in table 3. No patient in this study exhibited clinical symptoms of night blindness or visual abnormality, bone pain or fracture, excessive bleeding, or any metabolic sequelae associated with these fat-soluble vitamin derangements. However, one year after surgery, the incidence of secondary hyperparathyroidism was 20%, whereas 47% of the patients had elevated alkaline phosphatase levels (Table 4).

Fat-soluble vitamin	Type of operation		
	RYGBP/BPD (present study)	BPD/BPD-DS (reference 12)**	LRYGB (reference 9)
A	7.7%	52%	17%
25(OH)D_3	41.7%	57%	21%
D_3	50%	No data	No data
E	*	0%	No data
δ-tocopherol	11.1%	No data	No data
K_1	No data	51%	No data
K_2	27.3%	No data	No data

Table 3: *Incidence of fat-soluble vitamin deficiency, observed 1 year after different types of malabsorptive bariatric operations.*

**All patients were vitamin E deficient before and at all times after operation*

***As the preoperative vitamin levels were not measured in that study, the vitamin deficiency due to the operation cannot be distinguished from the total deficiency.*

	BPD/RYGBP	
	Before operation	1 year after operation
Vitamin 25(OH)D_3		
Normal levels (30 - 80 ng/ml)	12 (80%)	7 (46.7%)
Low levels	3 (20%)	8 (53.3%)
Total No. of patients	15	15
Calcium		
Normal levels (8.8 - 11.2 mg/dL)	14 (93.3%)	14 (93.3%)
Low levels	1 (6.7%)	1 (6.7%)
Total No. of patients	15	15
PTH		
Normal levels (10 - 65 pg/ml)	15 (100%)	12 (80%)
High levels	-	1 (6.7%)
Significantly high levels	-	2 (13.3%)
Total No. of patients	15	15
ALP		
Normal levels (34 - 104 U/L)	7 (46.7%)	8 (53.3%)
High levels	8 (53.3%)	7 (46.7%)
Total No. of patients	15	15

Table 4: *Numbers of patients that presented with deranged calcium metabolism before and 1 year after RYGBP/ BPD/surgery. Numbers in brackets correspond to percentage of patients in each group.*

PTH: Parathyroid Hormone; ALP: Alkaline Phosphatase.

Despite the desired weight-loss and resolution of co-morbidities achieved with malabsorptive bariatric operations, postoperative nutrient deficiencies are common and require exogenous supplementation and regular monitoring to maintain normal serum values [6-15]. While there is a lot of information on nutritional deficiencies for nutrients such as protein, iron, folic acid, calcium and water-soluble vitamins [6-10], the literature data concerning fat-soluble vitamin levels before and after bariatric operations are few and inconsistent. Slater., *et al.* found that the incidence of fat-soluble vitamin deficiency was 69% for vitamin A, 68% for vitamin K and 63% for vitamin D in obese patients by the fourth year after BPD or BPD/DS, with no change in vitamin E levels [12]. Contrary to that, Granado-Lorencio., *et al.* observed decreased levels of vitamin E, but no change in levels of vitamin A or D after RYGBP or BPD [21]. Dolan., *et al*. found that almost half of the operated patients had low vitamin A, D, and K levels BPD or BPD/DS surgery [22] and Madan., *et al.* observed abnormal vitamin A and 25(OH)D_3 blood levels both pre- and 1-year postoperatively in obese patients that underwent laparoscopic gastric bypass (LRYGBP) [9].

BPD/RYGBP is considered safer regarding the post-operative metabolic complications compared with other types of biliopancreatic diversion [10,11]. This is the first attempt to determine the effect of BPD/RYGBP operation on fat-soluble vitamin levels in a small group of patients. Based on our data, it seems that fat-soluble vitamin deficiencies one year after BPD/RYGBP surgery are lower compared with those observed one year after BPD, BPD/DS or LRYGBP operations (Table 3), verifying the potentially increased safety of BPD/RYGBP.

The decrease of serum 25(OH)D_3 levels was significant within the first year after BPD/RYGBP, in agreement with previous data in other types of BPD surgeries [1,12,22]. Although decreased 25(OH)D3 levels may be correlated with hypocalcemia, no such incidence was observed. However, secondary hyperparathyroidism was present in 20% of patients and 47% of patients exhibited elevated alkaline phosphatase levels despite calcium supplementation, possibly indicating problems with calcium metabolism in these patients.

It has been reported that there is a significant incidence of vitamin K deficiency after BPD or BPD/DS operations. Slater., *et al*. found the incidence of vitamin K deficiency to be 51% by the first year after PBD/DS [12], while Dolan., *et al.* found that half of the patients were deficient in vitamin K after BPD (37 months) or BPD/DS (23 months) [22]. Despite vitamin K deficiency, there is no reported evidence of altered clotting and increased bleeding tendency after bariatric surgery. Our data are in line with those published for other bariatric surgeries, showing decreased vitamin K levels postoperatively, with no apparent blood complications.

Our patients lost about 50% of their initial vitamin E levels during the first postoperative year. Based on this, as well as the lower than normal pre-operative levels measured, it seems important to consider normalization of vitamin E levels of super-obese patients even before the BPD/RYGBP surgical procedure, in order for these patients to be protected from possible complications. Slater., *et al.* suggest that serum vitamin E levels were normal in all patients at 1 year after BPD [12] and Dolan., *et al.* reported that only 5% of patients at an average of 28 months after BPD and BPD/DS had low levels of vitamin E [22]. However, in both these studies, the pre-operative levels of the patients included in the study were not measured; therefore, direct correlations with our data cannot be made. In line with our data, Granado-Lorencio., *et al.* observed decreased levels of vitamin E after RYGBP or BPD [21].

In contrast to all other fat-soluble vitamins, we did not find significant decrease of vitamin A levels one year after BPD/RYGBP bariatric surgery, in agreement with data from RYGBP or BPD bariatric surgeries [21]. In other types of bariatric surgeries, in different studies, there was a significant decrease of vitamin A levels ranging from 17% to 52% in patients underwent LRYGBP, BPD or BPD/DS one year after surgery [9,12]. The reason(s) for these discrepancies is unknown, and caution is needed regarding the levels of vitamin A after BPD/RYGBP bariatric surgery in the long-term.

Most of the obese patients in the present study had abnormal pre-operative levels of vitamin, which may be due to the altered biochemistry and metabolism of fat-soluble vitamins caused by obesity and its co-morbidities. For example, obese patients have high incidence of insulin resistance and type 2 diabetes [23], which has been connected to increased levels of serum retinol-binding protein 4 (RBP4) [24]. RBP4 binds vitamin A and this may explain its elevated levels observed in the present study. One the other hand, Desci., *et al.* found that median serum vitamin A levels in non-operated obese boys were lower compared to control values [25]. This discrepancy could be explained by the fact that serum concentrations of vitamin A are influenced by age, sex, diet and race [26].

Several studies report prevalence of vitamin D depletion among morbidly obese patients seeking gastric bypass surgery [27-30]. The reason for the elevated D_3 or normal 25(OH)D_3 serum levels measured in the present study is not known but are in line with the normal values of bone metabolism markers prior to surgery.

Vitamin E levels were measured to be lower than normal for all of the patients preoperatively, suggesting that vitamin E deficiency was already present in our patients before surgery. This vitamin E deficiency could be attributed to chronic oxidative stress of morbidly obese patients and it is in accordance with literature data, although there are only a few studies that have dealt with antioxidants and obesity. Lower serum levels of vitamin E have been found in subjects with abdominal obesity [30] and significantly lower vitamin E and β-carotene levels were measured in the plasma of obese compared to non-obese boys [31]. Reitman., *et al.* found that the levels of fat-soluble antioxidants, vitamin E and carotenoids were significantly lower in non-operated patients with severe obesity as compared to subjects with normal weight [32].

In the present study we measured only vitamin K_2 levels, which were found to be very high compared with those reported for normal weight individuals [33]. Although vitamin K levels have been measured in obese patients postoperatively [12,22], this is the first study to measure its levels in obese patients preoperatively. However, there are no reported complications related to increased levels of vitamin K in these patients, which may be explained by a possible balanced existence of other forms of vitamin K, such as K_1, in obese patients' blood serum.

Conclusions

Based on the results of the present pilot study, morbidly obese patients presenting for BPD/RYGBP bariatric surgery need both pre-operative and long-term post-operative monitoring of serum fat-soluble vitamin levels. This will permit: (a) the early diagnosis and correction to normal levels of any established fat soluble vitamin deficiency before patients' submission in BPD/RYGBP operation, (b) the administration of appropriate doses of multivitamin supplements to these patients, in order to prevent the surgically caused vitamin deficiencies to become of clinical significance. It is interesting to note that fat-soluble vitamin deficiencies observed one year after BPD/RYGBP surgery seem to be lower compared with those observed one year after BPD, BPD/DS or LRYGBP operations, although further studies are required in order to make final conclusions.

Conflict of Interest

The authors declare no conflict of interest.

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