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Original / *Vitaminas*

Fat-soluble vitamin deficiencies after bariatric surgery could be misleading if they are not appropriately adjusted

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Abstract

Objective: **To evaluate the differences in frequency of fat-soluble vitamin deficiencies if we adjust their levels by its main carriers in plasma in patients undergoing Biliopancreatic diversion (BPD) and Roux-en-Y gastric bypass (RYGB).**

Research Methods & Procedures: **We recruited 178 patients who underwent RYGB (n = 116 patients) and BPD (n = 62 patients) in a single centre. Basal data information and one-year after surgery included: anthropometric measurements, fat-soluble vitamins A, E and D, retinol binding protein (RBP) and total cholesterol as carriers of vitamin A and E respectively. Continuous data were compared using T-Student and proportions using chi-square test.**

Results: **There was a vitamin D deficiency of 96% of all patients, 10% vitamin A deficiency and 1.2% vitamin E deficiency prior to surgery. One year after surgery, 33% of patients were vitamin A deficient but the frequency reduced to 19% when we adjusted by RBP. We found a vitamin E deficiency frequency of 0% in RYGB and 4.8% in DBP one year after surgery. However, when we adjusted the serum levels to total cholesterol, we found an increased frequency of 8.7% in RYGB group for vitamin E deficiency and 21.4% in DBP (p = 0.04).**

Conclusion: **We have found a different frequency of deficit for fat-soluble vitamin both in BPD and RYGB once we have adjusted for its main carriers. This is clinically relevant to prevent from overexposure and toxicity. We suggest that carrier molecules should be routinely requested when we assess fat-soluble vitamin status in patients who undergo malabsorptive procedures.**

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Key words: *Bariatric Surgery. Vitamin. Fat soluble. BPD. Gastric bypass Roux.*

LAS DEFICIENCIAS DE VITAMINAS LIPOSOLUBLES TRAS LA CIRUGÍA BARIÁTRICA PUEDEN SER PERJUDICIALES SI NO SE AJUSTAN ADECUDADAMENTE

Resumen

Objetivo: **Evaluar las diferencias en la frecuencia de las deficiencias de vitaminas liposolubles si ajustamos sus concentraciones mediante sus principales transportadores plasmáticos en pacientes sometidos a derivación biliopancreática (DBP) y derivación gástrica en Y de Roux (DGYR).**

Métodos de investigación y procedimientos: **Reclutamos a 178 pacientes sometidos a DGYR (n = 116 pacientes) y DBP (n = 62 pacientes) en un único centro. Los datos de información basal y al año de la cirugía incluyeron: mediciones antropométricas, vitaminas liposolubles A, E y D, proteína de unión al retinol (PUR) y el colesterol total como transportadores de las vitaminas A y E, respectivamente. Los datos continuos se compararon utilizando la t de Student y para las proporciones el test chi cuadrado.**

Resultados: **Hubo una deficiencia de vitamina D en el 96% de todos los pacientes, de vitamina A en el 10% y de vitamina E en el 1,2% antes de la cirugía. Un año después de la cirugía, el 33% de los pacientes tenía deficiencia de vitamina A pero la frecuencia se redujo al 19% cuando ajustamos para la PUR. Encontramos una frecuencia de deficiencia de vitamina E en el 0% de los pacientes con DGYR y en el 4,8% de aquellos con DBP un año después de la cirugía. Sin embargo, cuando ajustamos las concentraciones séricas de colesterol total, encontramos un aumento de la frecuencia de hasta el 8,7% de deficiencia de vitamina E en el grupo con DGYR y del 21,4% en el grupo con DBP (p = 0,04).**

Conclusión: **Encontramos una frecuencia diferente de déficit de vitaminas liposolubles tanto en DBP como en DGYR una vez que ajustamos para sus principales transportadores. Esto es clínicamente relevante para evitar la sobreexposición y la toxicidad. Sugerimos que se deberían solicitar de forma rutinaria las moléculas transportadoras a la hora de evaluar el estado de vitaminas liposolubles en pacientes sometidos a procedimientos que entrañan malabsorción.**

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Introduction

Obesity and morbid obesity represent a growing worldwide serious health problem. It affects a significant percentage of young and adult population and is associated to chronic comorbidity[1].

Bariatric surgery is a procedure commonly used in the management of obesity with BMI greater than 40 or 35 kg/m^2 with comorbidities. It has been found to be the only effective long-term treatment for morbid obesity[2]. Multiple studies have shown weight loss and resolution or improvement of comorbidities after bariatric surgery.

Although the benefits have been proved in clinical trials, they are not exempt from several, mineral and vitamin deficiencies, mainly in intestinal bypasses procedures as biliopancreatic diversion and gastric bypass compared to restrictive techniques[3].

Several factors contribute to produce metabolic deficiencies, like reduced caloric intake, gastric volume reduction, gastrointestinal tract bypass and malabsorption, poor food tolerability and lack of compliance with oral supplementation. It also has been found that morbid obese population present with vitamin and mineral deficiencies even before surgery in a significant proportion. An explanation would be the lack of intake of enriched food in proteins, vitamins, minerals and fiber, and the abuse of high caloric density meals with poor nutritional value[4].

Fat-soluble vitamin deficiencies can lead to several disorders with different severity. Some of them are well known and highly prevalent, like vitamin D deficiency[5]. Other fat-soluble vitamin deficiencies vary in a range of dysfunction and severity, like vitamin A or E deficiency. Despite the lack of knowledge about the clinical implication of vitamin A deficiency after bariatric surgery, reports of cases have shown the occurrence of severe ophthalmic complications as corneal xerosis or night blindness, and dermopathy[6]. In addition the pathophysiology of vitamin E deficiency and its clinical implications are less known.

Objective

Although there are several publications on this topic, there is controversy about the different prevalence reported in literature about fat-soluble vitamin deficiencies in bariatric surgery and the best method for diagnosis and monitor treatment. Our hypothesis intends to illustrate that frequency of fat soluble vitamin deficiencies can vary if we adjust their levels to its carrier proteins.

Material and methods

Participants

We recruited retrospectively 178 patients who underwent Roux-en-Y gastric bypass (RYGB) (n = 116 patients; 65.1%) and biliopancreatic diversion (BPD) (n = 62 patients; 34.9%) in a single center, between january 2009 and march 2011.

Clinical and biochemical data were obtained from medical charts before surgery and one-year follow-up. All patients signed a written informed consent prior to surgery in which it was specified that clinical and analytical data collected before the bariatric procedure and during follow-up could be potentially used in an anonymous way for investigation and publication. This study was approved by the Ethics Committee of the Hospital Clinico San Carlos and was in compliance with the Helsinki Declaration.

Bariatric procedures

Eligibility for RYGB or DBP procedures varied according to the patients' clinical characteristics and comorbidities, evaluated by the coordinated team of endocrinologist and bariatric surgeon. All surgeries were performed laparoscopically in a single center. RYGP consisted of the creation of a small vertical gastric pouch of approximately 15-20 ml, a 150-200 cm Roux limb and a 50-100 cm biliopancreatic limb. BPD included two types of procedures: a classic duodenal switch (14 cases) and a single-anastomosis duodeno-ileal bypass with sleeve gastrectomy or SADI-S (48 patients). In the classic duodenal switch, a sleeve gastric resection was followed by a douodeno-ileal bypass with a 250 cm alimentary limb and a 75-100 cm common channel. SADI-S was performed as described previously[7]; it consisted of a one-loop duodenal switch in which after the sleeve gastrectomy (performed over a 54 Fr [18mm] bougie) and the duodenal division, the proximal duodenal stump was end-to-side anastomosed to the ileum at 250 cm form the ileocecal valve, thus creating a long biliopancreatic channel and a 250 cm common + alimentary limb. Because SADI-S is a simplified duodenal switch which has proved to behave in the same way as the classic duodenal switch, both techniques were considered under the BPD group for statistical analyses.

Examinations

Basal data information and one-year after surgery included: anthropometric measurements (height, weight, body mass index [BMI], calculated as weight (kg)/height (m^2), percentage weight loss [%WL]), fat-soluble vitamins A, E and D, and retinol binding protein (RBP) and total cholesterol as carriers of vitamin A and E, respectively. An absolute concentrations of fat-soluble vitamins as well the ratio vitamin A/RBP and vitamin E to total cholesterol were registered. The specific level for each deficiency were established at vitamin A < 0.30 mg/L, vitamin A/RBP < 0.65 mg/mg, vitamin E < 5.0 mg/L, vitamin E/cholesterol < 5.0 mg/g and 25(OH) vitamin D < 30 ng/mL.

Biochemical methods

Blood samples were collected after overnight fasting. After centrifugation serum was separated immediately, protected from light and frozen to -80ºC until analysis. Vitamin A and E measurements were performed with the use Liquid Chromatography of Chromsystems Diagnostics® (Munich, Germany) in a Shidmazu HPLC whit UV detection at 325 nm and 295 nm. The calibration standard is traceable to NIST 968e reference material. The interassay coefficient of variation was 6.4% and 7.17% for levels of 0.38 and 0.75 mg/L of Vitamin A, and for levels of 7.57 and 18.55 mg/L of Vitamin E was 5.3% and 5.4% respectively. The quality of the method is evaluated by UKNEQAS (United Kingdom National External Quality Assessment Scheme).

Total 25(OH) vitamin D was measured by a competitive direct Immunoassay through quimioluminiscency in a Liason analyzer (DiasSorin®, Saluggia, Italy). The method uses magnetic particles covered with a specific antibody anti-25(OH) vitamin D (solid phase) and conjugated 25(OH)vitamin D with an isoluminol derivate. The method has a functional sensitivity below 4 ng/mL, analytic range to 150 ng/mL, and the interassay coefficient of variation was 10.7% and 9.9% for levels of 17.43 and 112 ng/mL of 25(OH) vitamin D respectively. The quality of the method is evaluated by DEQAS (Vitamin D External Quality Assesment Scheme).

Total Cholesterol was measured in Olympus AU 5400® (Beckman Coulter Diagnostics. Brea, California, USA)with a cholesterol-oxidase method. The calibrator is traceable to NIST SRM 909b. The analytical range is 20-700 mg/dl and the quality of the method is evaluated by External Quality Program of SEQC (Sociedad Española de Química Clínica).

Retinol Binding protein is measured for Nephelometry in a BN Prospec (Siemens Diagnostic. Munich Germany).The analytical range is 1-20 mg/dl.

Statistical analysis

Descriptive results were expressed as mean ± standard deviation for continuous variables. Categorical variables were summarized as percentages and interquartile range (IQR).

The main outcomes was to evaluate the differences in the proportion for each fat-soluble vitamin deficiency between both groups of surgery (RYGP and BPD), at one year after surgery. Statistically significance differences for the main outcomes were determined in lineal regression models, with each vitamin concentration as the dependent variable and the type of surgery (RYGP or BPD), age, gender, weight, BMI one year after surgery and weight's percentage lost as independent variables. Continuous data were compared between groups using T-Student and proportions using chi-square test. The p values were two-sided and statistical significance was considered when $p < 0.05$. All statistical analyses were performed using the Statistical Package for Social Sciences, version 15.0 ((IBM SPSS Statistics Inc., Chicago, IL, USA).).

Results

Basal characteristics

Among the 178 patients evaluated, 48 (27%) were male and 130 (73%) were female with a mean age of 47 (11.8), ranging from 18 to 69 years old. The BMI before surgery ranged between 30.6 to 71.7 kg/m^2, with a mean of 44 (6) kg/m^2.

Patients were similar in age and BMI at baseline, with a higher proportion of female patients in gastric bypass group (RYGP) compared to biliopancreatic diversion (BPD) ($p < 0.001$) (table I).

Weight lost

Those patients in the group for the biliopancreatic diversion experienced a greater % WL than those in the bypass surgery group (37.2% *vs* 33.4%, $p = 0.012$) one year after surgery (table I).

Vitamin concentrations

Before surgery, the median concentration for 25(OH) vitamin D was 17.2 (IQR: 13.8-24.3) ng/ml. 98.2% of all patients had a 25(OH) vitamin D less than

Table I
Basal characteristics and weight changes after the bariatric procedures

Characteristics	*Roux-en-Y gastric bypass*	*Biliopancreatic diversion*	*P value*
Age (years)	45.28 ± 20.2	47.7 ± 13	.20
Women (%)	81.9	56.5	.001
BMI before surgery (kg/m^2)	43.7 ± 5.3	44.5 ± 7.3	.41
BMI 1 year after surgery (kg/m^2)	29 ± 4.6	28 ± 5.7	.28
Percentage weight loss	33.4 ± 8	37.2 ± 10	.012

BMI: body mass index.
Data presented as percentages or median ± standard deviation.

30 ng/ml considered as insufficient. One year after surgery, all patients in both groups needed supplementation with 25OH-vitamin D (oral calcifediol 16.000 U periodically as needed) for insufficient vitamin D levels.

Before surgery 10% of patients presented with vitamin A deficiency (absolute or adjusted ratio levels), whereas vitamin E deficiency was almost imperceptible affecting only 1.2% of patients.

In relation to vitamin A concentration, we observed a considerable frequency for vitamin A deficiency one year after surgery when we measured the absolute serum levels of Vitamin A (< 0.30 mg/l); with a frequency of 27,5% in RYGB group and 38,1% in DBP group ($p = 0.14$). When vitamin A levels were adjusted to RBP (vitamin A/RBP < 0.65 mg/mg) the frequency diminishes to 17.4% in RYGP and 21.4% in DBP ($p = 0.58$).

Only two patients (1 in each group) presented with severe deficit for vitamin A/RBP one year after surgery, considered as less than 0.55 mg/mg. Most patients with deficiency had serum levels considered as mild (> 0.60 mg/mg).

We also found a vitamin E deficiency (< 5.0 mg/l) frequency of 0% in RYGB and 4.8% in DBP one year after surgery ($p = 0.06$). However, when we adjusted the serum levels to total cholesterol (vitamin E/cholesterol < 5.0 mg/g), we found an increased frequency of 8.7% in RYGP group for vitamin E deficiency and 21.4% in DBP ($p = 0.059$). We have found statistically significance differences in vitamin E deficiency before and after adjustment for total cholesterol in RYGB ($p = 0.04$) and in DBP ($p = 0.04$) (fig. 1).

Only 1 patient in DBP presented with serum level for vitamin E/Chol considered as severe (< 4.0 mg/g), being most of them (86.6%) considered as mild (4.5-4.9 mg/g).

Discussion

Although bariatric surgery is a highly effective procedure for the treatment of obesity and morbid obesity, it may be associated with some nutritional and metabolic deficits. Among them, fat soluble vitamins deficiencies are prevalent due to inadequate intake and/or malabsorption and alteration of its normal metabolism. Once, the deficit was established, it is mandatory to supplement and replace it in a safe and effective way. Vitamin A, E and D are not exempt from side effects and toxicity if they are not properly indicated and monitored along the follow up.

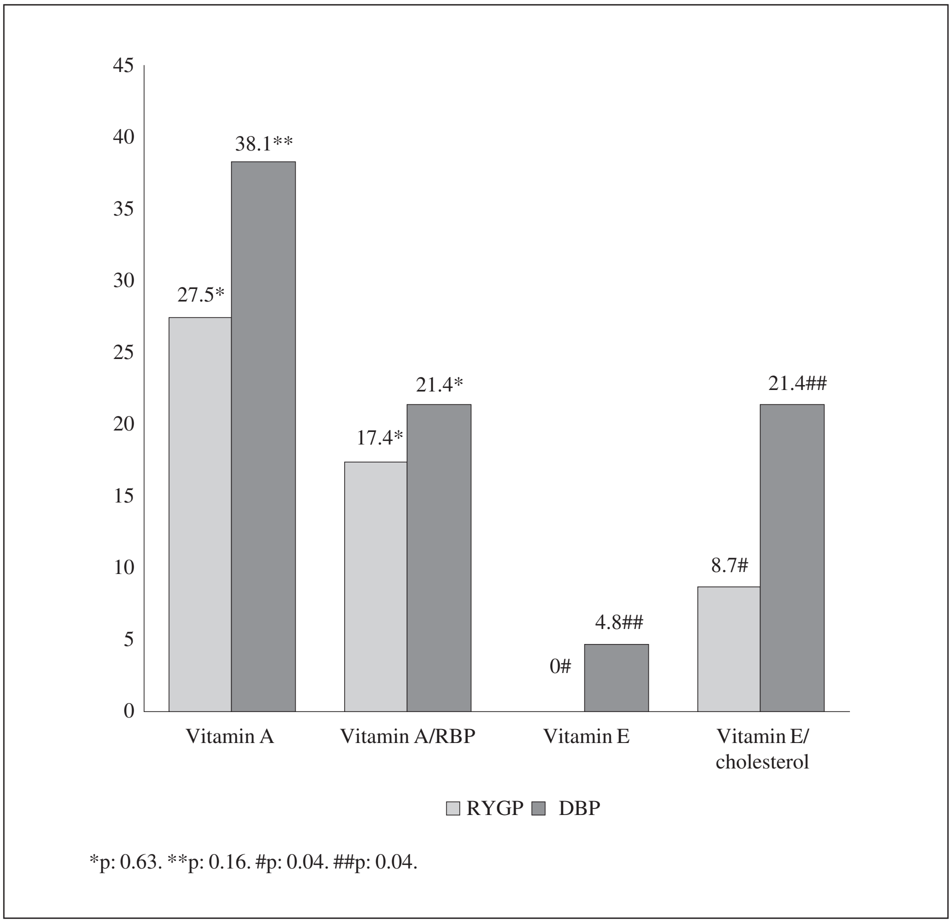

Fig. 1.—Percentage for fat-soluble vitamin deficiency one year after surgery (%) both absolute and adjusted by main molecule carrier.

Eventually, restrictive procedures could associate fat soluble vitamin deficiencies due to decreased oral intake, avoidance of certain meals as a result of digestive intolerance and protein carrier deficits; although the literature doesn't support this firmly[8]. We have evaluated those patients at higher risk for fat-soluble vitamin deficiency, such as those that occur in patients who underwent RYGB and DBP.

Several factors contribute for fat-soluble vitamin deficiency risk. Poor nutritional status before surgery, aggravated by diminished oral intake contribute to preoperative deficit. After surgery, the decreased intake due to reduced stomach poach and malabsorptive intestinal bypass or diversions, are the main mechanisms for fat soluble vitamin deficiency.

The prevalence of (25OH) vitamin D deficiency in general population is proven to be high ranging from 4 to 39% in Europe, with a lower limit level between 25-30 ng/ml in different studies[9]. Obese population is at high risk for 25(OH) vitamin D deficiency due to reduced bioavailability as it is placed in adipose tissue[10]. There is a double vitamin D origin: a significant proportion is produced in skin from cholesterol and ultraviolet radiation, and a smaller proportion comes from fish, eggs, dairy products, cereals, oils and meat. In Spain, 81.6% presented vitamin D intake under dietary references[11].

In our series, there is a high frequency (99.2%) for (25OH) vitamin D deficiency prior to surgery and a need for oral supplementation due to levels under 30 ng/ml in all patients after surgery. This is consistent with other results previously reported, as published by Ducloux et al in France and Moizé et al in Spain, who found a high prevalence for vitamin D deficiency of 96% and 94% before bariatric surgery, respectively[10,12].

We have found a result of 10% of patients presenting a vitamin A deficiency prior to surgery both absolute and corrected for RBP, similar to other series[4]. This represents an adequate nutritional status prior to surgery and the most likely cause of this deficiency would be a decreased intake in vitamin A. Prior to surgery, in the absence for protein malnourishment with adequate RBP and prealbumin levels, absolute vitamin A levels may be equally valid.

In contrast, an important frequency for vitamin A deficiency one year after surgery was detected. Since malabsorptive procedures began to be performed, both patient series and clinic cases have been published for vitamin A deficiency[13]. However, according to medical literature, the range for this deficiency is very wide. Clinical signs and symptoms for severe vitamin A deficiency such as night blindness, xeroftalmia and hyperkeratosis are infrequent in this population[14].

In our sample, 33% of patients had vitamin A deficiency, when taking into account the absolute vitamin A levels, whereas if they are adjusted to RBP, the percentage of deficiency is reduced to 19% of subjects. After surgery, any disturbance that could associate protein malnourishment (intercurrent disease such infection, extended fasting or chronic diarrhea) can present with short half-life protein deficiencies; like RBP or prealbumin. Therefore, we should confirm vitamin A deficiency once we have adjusted for RBP[15], so we avoid overtreatment and risk of toxicity.

According to these findings, 36.7% of patients in RYGB group and 43.8% in DBP would have been incorrectly diagnosed with vitamin A deficiency if we only consider absolute levels of vitamin A. This represents an important overestimation with clinical relevance, as it implies potential treatment with high doses of vitamin A supplementation. When chronically administered, toxicity can associate ataxia, alopecia, hyperlipidemia, hepatotoxicity, bone and muscle pain, teratogenia during the first trimester of pregnancy, visual impairment or increased bone fractures due to osteoporosis among others[16].

Some prior publications have assessed the relationship between obesity and vitamin A deficiency, both pre and postoperatively[17,18]. Pereira et al. reported a prevalence of 14% for vitamin A deficiency preoperative in a cohort of morbid obese patients and 52% three months after gastric bypass, measuring retinol in serum while patients were being supplied with 5,000 IU of retinol acetate. In patients who underwent RYGB in our series, the frequency for vitamin A deficiency was substantially lower (17.4%) one year after surgery, once we have corrected for its main carrier protein (RBP). Slater et al. also found a high prevalence for vitamin A deficiency after DBP; in fact, 69% of patients had low vitamin A levels. In contrast with these results, we have found a frequency for vitamin A deficiency in DBP of 38%, which reduces to 21% once we have adjusted for RBP. The lack of adjustment for vitamin A carrier protein could be one of the main reasons for the discrepancies between results in literature.

Finally, we have observed a significant frequency for vitamin E deficiency once adjusted by total cholesterol. Vitamin E status after bariatric surgery is less known, although the clinical manifestations of this deficit are uncommon. The data published before range between 4-10% in different series[19,20]. In fact, a significant increment of this deficiency both in RYGB and DBP took place after cholesterol adjustment. This has clinical impact, as many patients are on treatment for hypercholesterolemia and others have low cholesterol levels due to malabsorption and decreased oral intake. Therefore vitamin E levels could be underestimated incorrectly. The clinical impact of vitamin E deficiency in these patients is unknown and there are not general recommendations for oral supplementation. Most patients in our series had mild deficiency which is easily supplemented with a daily dose between 200-400 mg of alpha-tocopherol.

Conclusion

Our data suggest that when vitamin A and E are evaluated, they must be adjusted by their carrier molecules to avoid incorrect interpretations, and thereby to prevent from overexposure and toxicity. We suggest that carrier molecules should be routinely requested to assess fat-soluble vitamin status in patients who undergo malabsorptive procedures.

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