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Review Article

Nutritional Status of Vitamin A in Morbid Obesity before and after Roux-en-Y Gastric Bypass

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Abstract: The objective of the present study was to identify the factors which contribute to the appearance and/or aggravation of Vitamin A Deficiency (VAD) in individuals with morbid obesity in the pre- and postoperative stages of Roux-en-Y gastric bypass (RYGBP). Bibliography searches were done in the data-bases of Medline and Lilacs, published in the last 35 years, priorizing the studies which assessed VAD through serum levels of retinol. The principal factors identified as contributors to VAD were oxidative stress, deficiency of other nutrients, lipid malabsorption in the postoperative stage, insufficient intake of lipids and food sources of Vitamin A, and presence of nonalcoholic fatty liver disease. The investigation of the nutritional status of Vitamin A in those individuals may foment intervention strategies easily incorporated in already established routine procedures, aiming to reduce VAD rates, which will reflect upon those individuals' quality of life.

Key words: Vitamin A, morbid obesity, obesity surgery, Roux-en-Y gastric bypass, zinc

Introduction

Obesity is a widespread disease of rising prevalence which has been acquiring epidemic proportions, being one of the principal public health issues in modern society.[1] Morbid obesity is one of the diseases which presents the highest mortality rates in the world. In Latin America, it is probable that 200,000 people die every year due to the associated co-morbidity. Mortality rate for morbid obesity is 12 times higher in males in the 25-40 age range when compared with normal-weight individuals.[2]

A recent longitudinal study found that the highest rise in the prevalence of obesity in the last decade was in class III or morbid obesity.[3] The clinical approach is generally ineffective in those cases, and bariatric operations are the most effective treatment leading to significant improvement in co-morbidities.[4] However, metabolic disorders derived from the surgical procedure may cause nutritional disorders, such as protein-caloric malnutrition.[5] Macronutrient deficiency is frequently associated with that of micronutrients, leading to the development of anemia, bone demineralization, and several hypovitaminoses.

Deficiency of vitamin A (VAD) is one of the most prevalent public health issues in the world, resulting in damages to the health of individuals affected by it, including death.[6] Vitamin A, besides participating in several primordial functions in the human organism, such as visual acuity, immunological activity, cellular proliferation and differentiation,[7] has recently received attention due to its action against free radicals, protecting the organism against oxidative stress. Consequently, vitamin A prevents tissue injury related to several nontransmissible chronic diseases, where obesity stands out because its prevalence has been significantly rising.[8]

The present review has as its objective to identify the principal factors which may contribute to the

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appearance and/or aggravation of VAD in individuals with morbid obesity in pre- and postoperative stages of Roux-en-Y gastric bypass (RYGBP), aiming to emphasize this nutritional condition and to help elaborate intervention strategies.

Materials and Methods

This is a bibliographic review of the data-bases of Medline and Lilacs from 1972 to 2006. The terms used in the bibliographical search were *obesity*, *morbid obesity*; *Roux-en-Y gastric bypass*; *micronutrient deficiency* and *vitamin A deficiency*, in English and Portuguese. From the available abstracts, we selected studies performed in humans, those found in their totality, published in the last 35 years, and we included studies of transverse, case-control, cohort and review types. We priorized the studies which assessed VAD through the serum retinol levels, excluding articles published in other languages, studies with animals, studies in vitro, and nonconclusive studies.

In the present review, we approached VAD in morbid obesity and after bariatric surgery for weight control and co-morbidity improvement. Principal nutritional deficiencies resulting from the surgical treatment, especially vitamin A, were studied for possible factors which may contribute to VAD in the pre- and postoperative stages.

Roux-en-Y Gastric Bypass and Nutritional Deficiencies

The advance of scientific knowledge regarding the rise of morbidity-mortality rates emphasizes the necessity of medical intervention against obesity. Operations for morbid obesity are justified as the only method which controls obesity both in the medium- and in the long-term.[9]

The SOS study,[10] which compared 845 patients submitted to bariatric surgery with 845 patients with medical treatment in a 10-year follow-up, reported a significant improvement in co-morbidities in patients submitted to RYGBP: from 64% to 100% (100% average) with respect to diabetes, from 25% to 100% (89% average) with respect to hypertension, and from 60% to 100% (88% average) with respect to dyslipidemias.

RYGBP has the potential to generate metabolic disorders, taking into account the reduction of the gastric reservoir with consequent hypochlorhydria and the enteric deviation (total exclusion of the duodenum and of the proximal jejunum with significant reduction of digestive enzymes), leading to macro- and micronutrient deficiency. According to Grace,[11] patients maintain a food consumption between 600 and 900 kcal which, if not well monitored, may cause serious nutritional deficiencies.

These deficiencies occur mainly due to malabsorption secondary to the decrease of GI tract segments where nutrients are absorbed. It is possible that besides this, the deficiency of some nutrients may occur due to decrease in intake and to the tendency to avoid foods postoperatively because of GI intolerances, like dumping syndrome. The prophylactic use of nutritional supplements may avoid these deficiencies.[12]

While the magnitude of these deficiencies is not certain, due to the lack of specific recommendations for supplementation for this group, frequently these metabolic disorders are not diagnosed.[12] Brolin and Leung[13] observed a large variation in the requests for laboratory tests and use of supplements in a study with 109 bariatric surgeons. Not all of those interviewed prescribed multivitamin supplements and the incidence of post-RYGBP nutritional deficiencies was considered to be underestimated.

Most of the literature on bariatric surgery nutritional deficiencies consists of case reports and retrospective reviews, and there are only a few prospective studies in this area.[12] Most frequent deficiencies are hypoproteinemia, iron deficiency anemia, hypocalcemia, and that of liposoluble vitamins.[13]

Only a few RYGBP studies report micronutrient deficiency postoperatively.[14,15] The reports embrace a limited number of micronutrients such as calcium, vitamin D, iron, and vitamin B_{12}.[15]

A few studies have reported VAD after RYGBP. Brolin et al[16] observed that the prophylactic supplementation of Vitamin A after RYGBP did not prevent this micronutrient deficiency in 10% of the patients after 4 years. There are studies demonstrating VAD after biliopancreatic diversion, even with the daily utilization of supplements of this vitamin.[15] Although there is not much knowledge regarding clinical consequences of VAD after bariatric surgery, some case reports have indicated the occurrence of ophthalmologic complications such as night blindness and cornea xerosis.[17]

Contributing Factors to VAD in Morbid Obesity, before and after RYGBP

1. Oxidative Stress

Oxidative stress may be defined as the adverse effects of oxidative reactions induced by free radicals inside the biological systems, causing lesions in relevant molecules such as DNA, proteins, carbohydrates, and lipids. It is a condition where oxidant metabolites exert their toxic effects either due to increased production or from disorders in cellular protective mechanisms.[18]

Insulin resistance is implicated in the increase in oxidative stress.[19] Paolisso et al[20] found positive correlation between plasma levels of reactive oxygen species and insulin. Orzechowski[19] reported that one of the most dangerous complications of insulin resistance is the increase in the susceptibility of muscle and cardiac cells provoked by oxidative stress.

Dyslipidemias are also implicated in the increase in oxidative stress. Individuals with dyslipidemia possess higher levels of lipid peroxidation. With the aim of evaluating the hypothesis that low HDL concentrations interfere with lipoprotein oxidation, Toikka et al[21] found significantly lower levels of oxidation of LDL in the group with high HDL levels, when compared to the one with low HDL levels. They concluded that constant low HDL levels are related to an increase in oxidative stress.

Retinol and carotenoids stand out as substances which act against the oxidative attack of oxygen. Studies demonstrate that carotenoids effectively participate in antioxidant defense, promoting the elimination of the singlet oxygen involved in the oxidative attack to nucleic acids, amino acids and polyunsaturated fatty acids. Therefore, retinol and carotenoids reduce NO synthesis through action on the iNOS, decreasing the production of oxygen-reactive species.[22]

Hence, adequate intake of vitamin A, particularly carotenoids, is important for the protection against the oxidative attack of free radicals to cell membranes, reducing the oxidative damage and therefore preventing the occurrence of nontransmissible chronic diseases.[23]

Serban et al[24] observed that individuals with dyslipidemia and glycemic levels higher than 200 mg/dL presented higher levels of lipid peroxidation. They concluded that the association between dyslipidemia and hyperglycemia, high levels of lipid peroxides and decrease in antioxidant capacity are implicated in the increased risk for development of cardiovascular attacks. Therefore, both hyperglycemia and dyslipidemias, factors commonly present in obese individuals, tend to increase lipid peroxides, which indicates a decrease in serum antioxidant levels, such as beta-carotene.

The literature has shown the association between BMI and serum levels of retinol and carotenoids. Viroonudomphol et al[25] found a negative correlation between BMI levels and those of serum retinol in a study performed with overweight and obese patients. Souza et al[26] verified a statistically significant decrease in the serum levels of carotenoids accompanying an increase in BMI, obesity being the nutritional condition mostly associated with low levels of carotenoids.

2. Deficiency of Other Micronutrients

Obese individuals present a tendency to consume larger quantity of foods of high energetic density (mainly with high content of lipids) and relatively lesser quantity of foods of low energetic density (such as fruits and vegetables), compared with non-obese individuals. In the context of nutritional transition, the process of industrialization, besides favoring sedentary lifestyles, has reduced the cost and increased the accessibility to foods low in vitamins and minerals and with a high content of energy and fat, especially saturated.[27] Thus, it is possible to verify the presence of micronutrient deficiency, even if subclinical, characterizing the "hidden hunger", accompanying the rise in obesity. Frequently, deficiencies of vitamins and minerals occur in a combined manner because of the association between food sources, metabolic routes and physiological functions, in such a way that multiple deficiencies may be disguised by a higher deficiency of one micronutrient. Some nutrients are prominent in their relationship with vitamin A, such as zinc and iron.[28]

Zinc nutritional status influences vitamin A metabolism in many aspects, including its absorption, transport and utilization. On the other hand, there is also evidence that vitamin A has influence on the absorption and utilization of zinc.[29] Two mechanisms are accepted to explain the interrelationship between those two micronutrients. One is related to the regulatory role of zinc in the transport of vitamin A, mediated by the synthesis of proteins. Zinc deficiency may

decrease the synthesis of retinol-binding protein (RBP) in liver and may lead to low concentrations of RBP in plasma. Another proposed mechanism is the conversion of retinol into retinaldehyde, which requires the action of the dehydrogenase retinol enzyme, which is dependent on zinc.[30] Zinc can also affect the absorption of vitamin A. Zinc deficiency reduces the lymphatic absorption of retinol in rats, which may be attributed to the lower exit of lymphatic phospholipids, resulting from the decrease in bile secretion in the intestinal lumen.[31]

A relationship seems to exist between the nutritional status of zinc and vitamin A in patients with pathological conditions which might compromise liver function, such as cirrhosis, cystic fibrosis and idiopathic hemochromatosis.[29] Yet, there are no studies relating zinc and vitamin A deficiency to nonalcoholic fatty liver disease, a common condition in morbid obesity. Cominetti et al[32] observed zinc deficiency in 71% and 68% of RYGBP patients pre- and postoperatively. The percentage of zinc intake 2 months after RYGBP was 31% of the adequacy of zinc ingestion, showing that with the reduction in food intake it is not possible to guarantee adequate intake of this nutrient. Neve et al,[33] in spite of not having determined serum levels of zinc, observed a prevalence of ~36% alopecia 6 months after vertical banded gastroplasty. Zinc deficiency may be one more of the many contributing factors to VAD in bariatric patients.

A possible relationship also exists between VAD and anemia. Vitamin A participates in iron metabolism at several stages, among them iron intestinal absorption, transport in serum, release of iron in liver stores, mobilization of iron to bone marrow, and hemoglobin synthesis. The availability of iron for hematopoietic tissue synthesis is inhibited during VAD. Conversely, iron influences the bioavailability of vitamin A. The function of the intestinal mucosa is compromised by iron deficiency, which makes the absorption of vitamin A from alimentation difficult. Jang et al[35] demonstrated that iron deficiency causes reduction in plasma retinol levels due to lower mobilization of vitamin A by the liver, besides damaging the absorption and utilization of this vitamin. The lower mobilization of vitamin A by the liver may lead to a reduction in the plasma pool of retinol. Likewise, the plasma levels of RBP are low in iron deficiency.

The presence of iron deficiency has been demonstrated in 20 to 49% of patients who underwent RYGBP, with a higher incidence in females.[13] Patients submitted to RYGBP are particularly vulnerable to iron malabsorption, because the duodenum and proximal jejunum, which are the largest sites of absorption of this nutrient, are excluded from the normal digestive traffic. Besides, iron absorption is severely limited by achlorhydria resulting from the decrease in stomach size.[12]

3. Mal-digestion and Absorption after RYGBP

In RYGBP, exclusion of the duodenum and of the first 100 cm of jejunum from food traffic decreases the area of the sites of vitamin A absorption. The pre-formed vitamin A absorption occurs in the intestinal lumen where retinol esters from the diet (mainly retinyl palmitate) are emulsified with biliary salts and hydrolyzed to retinol by several pancreatic enzymes and retinyl ester hydrolases (REH), before its absorption.[36]

In physiological concentrations, the retinol absorption is mediated by a saturable carrier, whereas in pharmacological levels, absorption is made by passive diffusion. In the enterocyte, retinol binds to cellular retinol binding-protein II (CRBPII) and complex retinol is esterified by lecithin retinol acyltransferase (LRAT). When large quantities are absorbed and CRBPII becomes saturated, free retinol esterification is performed by acyl CoA-retinol acyltransferase (ARAT).[36,37]

Retinyl esters are incorporated into the chylomicrons, which enter the lymphatic circulation and migrate to the blood circulation where several biochemical processes, such as hydrolysis of triacylglyceroids and exchange of apoproteins, occur, resulting in *remaining chylomicrons* (RC). In this conversion, the quantity of retynil esters remains almost unaltered until the chylomicrons reach the liver.[36] About 50 to 90% of the ingested retinol is absorbed and transported to the liver by the RC in the form of retinyl esters. Although the liver is the principal destiny of the RC, their extrahepatic absorption may be an alternate route of retinol absorption to other tissues, such as bone marrow, adipose tissue, skeletal muscle and kidneys.[36,38]

Carotenoids with activity of pro-vitamin A are also solubilized in the micelle in the intestinal lumen and, next, are absorbed by passive diffusion.[7]

In the enterocyte, these carotenoids may be converted into Vitamin A, metabolized to inactivated species, incorporated into RC, and they can pass to the lymphatic circulation intact or remain restrained in the cell until their descaling.[38]

The absorbed beta-carotene may be converted into vitamin A in the enterocyte by the beta-carotene 15,15'-monooxygenase enzyme (BCO), previously known as beta-carotene 15-15'dioxygenase. The central cleavage of beta-carotene by this enzyme will result in two molecules of retinal.[38] CRBPII directs the reduction of retinal to retinol and its subsequent esterification in retinyl esters to be incorporated into RC and exported from the intestine.[36]

The liver, lung, adipose tissue and other tissues also possess this enzyme, indicating that the conversion of beta-carotene into vitamin A may occur after its absorption by the liver and by the extrahepatic tissues.[7]

4. Lipid Intake and Food Sources of Vitamin A after RYGBP

The reduction in alimentary intake with frequent lipid restriction in the postoperative stage, including decrease in consumption of food sources of vitamin A, can also be a contributing factor to VAD in this group.

The remaining stomach after RYGBP has a volume of 30 to 50 ml. Thus, in the immediate postoperative period, restricted liquid intake, evolving to a complete liquid diet is given until discharge from hospital. Intake in the first 15 days consists of a liquid diet of small volumes (~50 ml at each meal) and has as its main objective gastric rest, adaptation to small volumes, and hydration. The following stage involves the introduction of pasty foods to avoid gastric distension, progressing to solid alimentation 12 weeks after surgery.[39]

Only after the third month after RYGBP does the gradual evolution occur to a consistency close to the ideal for satisfactory nutrition, where almost all foods are introduced in the diet. In this phase, foods with high fiber consistency are not tolerated. Generally, a diet with normal consistency, with the introduction of all foods, occurs around the fourth month after the surgery.[39]

Meats and meat products, leafy vegetables, bread and other foods may be rejected because they need prolonged mastication. Another group of foods frequently rejected is milk and its derivatives, which are easy to swallow, but which are not tolerated by these patients;[39] this can contribute to a low intake of vitamin A, because preformed vitamin A or retinol is found in animal sources, like liver, milk and its derivatives and, in a lower proportion, in yolk. On the other hand, sources of provitamin A, ie. carotenoids, are dark-green and yellow-orange vegetables.[36]

Also, the lower fat absorption after RYGBP, makes restriction of fats in the diet necessary, which also may compromise vitamin A intake and absorption. Lipid intake, parallel to vitamin A intake, is of extreme importance for this vitamin absorption.[40]

5. Liver Insufficiency – NAFLD

Nonalcoholic fatty liver disease/Nonalcoholic steatohepatitis (NAFLD/NASH) is present in >90% of patients with morbid obesity and entails a spectrum of pathologic disorders that vary from simple steatosis to steatohepatitis, fibrosis and cirrhosis.[41] Although the complete mechanism of NAFLD pathogenesis is still to be clarified, it has been observed that insulin resistance (IR) and the oxidative stress play a fundamental role in it. IR may favor the mobilization of fatty acids of peripheral adipose tissues and the increased absorption of fatty acids by the liver. Moreover, hyperinsulinemia blocks the mitochondrial oxidation of fatty acids with an increase of triglycerides and free fatty acids in the liver.[42]

Reduction in the serum levels of retinol is frequently found in patients with liver insufficiency and may be explained by the reduced storage of vitamin A, or by the synthesis and/or decreased release by the liver of the binding proteins and cellular transport, among other causes.[43] The deficient enzymatic conversion of beta-carotene into retinol, which also occurs in the liver, might be involved in the decrease in the serum levels of retinol.[7]

The oxidative stress present in liver disease may be one more factor involved in the reduction of the serum levels of vitamin A. Rising evidence suggests that the increased production of free radicals and/or the decrease in the antioxidant defenses are remarkable characteristics of liver disease of any etiology. Mitochondria, enzymes of the cytochrome P450, Kupffer's cells and neutrophils are the principal sources of reactive species of oxygen in hepatocytes.[44]

The production of reactive oxygen species promotes the activation and transformation of stellate cells into cells with the phenotype of myofibroblasts, which are responsible for the synthesis of col-

lagen.[44] The activation and transformation of these cells are associated with the decrease in their storage of vitamin A. The reduction in the storage of vitamin A may have a causal role in this cellular transformation, because in cell culture, it was demonstrated that retinol and, mainly retinoic acid, could reduce the proliferation of these cells, as well as the synthesis of collagen and the transformation into cells of the myofibroblast type.[45]

Several factors are involved in the etiopathology of VAD in patients with liver disease, which may be related to the cause of this disease. Such factors are: decrease in the synthesis of protein carriers of retinol; decrease in food ingestion, and indirectly, that of vitamin A; deficiency of other micronutrients, such as zinc; decreased conversion of pro-vitamin A into vitamin A; oxidative stress; and portal hypertension.[44]

Final Considerations

Taking into consideration the collective dimension of VAD, reflected in the appearance/aggravation of co-morbidities related to obesity, and having as a basis the presented studies, the precocious identification of individuals at risk or with deficiency of vitamin A is fundamental. Thus, investigation of the nutritional status of vitamin A in individuals with morbid obesity in the pre- and postoperative stages of RYGBP can foment intervention strategies easily incorporated in the routine procedures already established, objectifying the eradication or at least the reduction of VAD rates and consequently reflecting upon these individuals' quality of life.

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