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Review Article

METABOLIC AND ENDOCRINOLOGICAL FACTORS RELATED TO NEPHROLITHIASIS PRE AND POST MULTIPLE TECHNIQUES OF BARIATRIC SURGERY: A SISTEMATIC REVIEW

Fatores endócrinos e metabólicos relacionados à nefrolitíase pré e pós técnicas diversas de cirurgia bariátrica: uma revisão sistemática

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HEADINGS - Nephrolithiasis. Bariatric surgery. Obesity. Hyperoxaluria. Gastric bypass.

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DESCRITORES - Nefrolitíase. Cirurgia bariátrica. Obesidade. Hiperoxalúria. Derivação gástrica.

ABSTRACT - ***Introduction***: Despite of benefits of bariatric surgery for obesity treatment, the procedure may be related to some complications. ***Aim***: Analyze studies to address the relation between nephrolithiasis and bariatric surgery. ***Methods***: Ten papers about this theme were selected from 2005-2013 in Pubmed, describing the relation of nephrolithiasis or their risk factors with several types of bariatric surgery. ***Results***: Retrospective studies with minimal follow-up of three years demonstrated 7,65% in surgery patients and 4,63% non-surgery with nephrolithiasis (p<0,05). Prospective studies (8 of 10) revealed large percentage of calculi appearing and significant increase in oxaluria. ***Conclusion***: There is correlation between obesity surgery and nephrolithiasis.

RESUMO – ***Introdução***: Apesar dos benefícios das operações bariátricas para o tratamento da obesidade, elas podem acompanhar algumas complicações. ***Objetivo***: Analisar estudos que enfoquem a relação entre nefrolitíase e procedimentos cirúrgicos bariátricos. ***Métodos***: Foram selecionados 10 estudos de 2005 a 2013 no PubMed que descreviam a relação de nefrolitíase ou seus fatores de risco com diversas técnicas de cirurgia bariátrica. ***Resultados***: Estudos retrospectivos, com seguimento por no mínimo três anos, demonstraram que 7,65% dos pacientes operados e 4,63% dos não operados apresentaram nefrolitíase (p<0,05). Estudos prospectivos (8 dos 10) verificaram grande porcentagem de aparecimento de nefrolitíase ou aumento significativo na oxalúria. ***Conclusão***: Os estudos mostraram que há relação entre operações para obesidade e nefrolitíase.

INTRODUCTION

The obesity prevalence in the Brazilian population has increased over the years; it has changed from 9.3% in 1989 to 14.8% in 2009. WHO estimates that 500 million people were obese in 2008, it means 100 million more than the number for 2006. Another estimate, also made by WHO, says that in 2015 there will be 700 million.[1,2] This indicates that an increasing percentage of people are subject to the comorbidities related to obesity, which 5.7% are believed to be morbid obese, in other words, they have a BMI≥ to 40 kg/m^2 and need surgical treatment[12,22].

Some publications about bariatric surgery patients started to come out on 2005; they pointed reduction on the prevalence of diabetes mellitus, hypertension, cardiovascular diseases and death, but also enhancement on nephrolithiasis' risk, hypothesizing that the procedure could be a risk factor for lithogenesis, which has been confirmed[16,18]. The relation between bariatric surgery and nephrolithiasis has been pointed as an important matter to be explored, since research remains scarce[4].

This article is a systematic review about the nephrolithiasis prevalence in patients who underwent different types of weight loss surgery, trying to establish its influence on this comorbidity.

METHODS

Search strategy

The literature review was performed during November 2013. Search was conducted in the PubMed electronic database using the following search phrase: ("Obesity") AND ("Nephrolithiasis") as title words or MeSH terms. The main goal was to identify relevant studies describing the prevalence of nephrolithiasis in obese patients. Among these, were searched articles that showed correlation of different bariatric surgery techniques to the theme.

Study selection

Initially, titles and abstracts were analyzed, and original studies that seemed to report obesity and nephrolithiasis as main subject were pre-selected, it means 112 articles. The studies that described the incidence of nephrolithiasis or its relation to different bariatric surgeries were selected, reaching 10 studies. Three researchers examined the full texts of the selected studies.

Studies that met the following criteria were selected: original article, English language, published between 2005 and 2013, full text available at Capes periodic, reports the occurrence of nephrolithiasis or its supporting emergence factors. Review articles, commentary, editorials, duplicate articles or sample size smaller than nine patients were excluded.

All potential differences in interpretation between the reviewers were discussed, to ensure that all the articles reviewed presented a satisfactory level of evidence.

Identified studies and handling of missing data

The literature search described above yielded 341 studies. A total of 10 articles were abstracted and included in the systematic review. Figure 1 shows the results of initial searches for inclusion.

If a study failed to report any of the variables, this was classified as "not reported." It was then analyzed the results comparing only the available data.

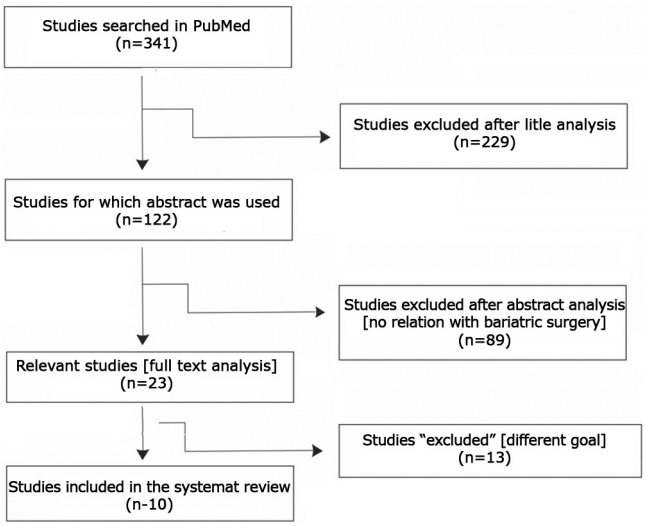

FIGURE 1 - Flow diagram for this systematic review

RESULTS

All studies were based in the USA between 2005 and 2013. Among 10 studies selected, three were retrospective made by ambulatory data analysis, and seven prospective following patients after surgery only or since a period before the surgery. Prospective studies have low number of patients when compared to the retrospective; 98% of the subjects were in the retrospective analysis (Table 1).

The 10 selected studies included a total of 9,944 subjects, 5,250 (52.7%) underwent bariatric surgery, the others 4,694 patients (47.3%) were obese used as comparison by some.

Among the patients who had undergone surgery, 4,798(91.3%) were by the Roux-en-Y gastric bypass (RYGB) technique.

Five studies showed the occurrence of nephrolithiasis, from these three reported supporting factors with different ratios. Other three didn't report the genesis of calculi, but increased excretion of calcium oxalate, for example. The remaining two studies didn't show the calculus genesis or any supporting evidence.

The aspects that possibly determine big differences in results are explained in the discussion.

DISCUSSION

Several studies of population basis have shown that obesity is an independent risk factor for the development of chronic kidney disease and kidney insufficiency. Fox et al.[9] studying the Framingham, MA., population, identified a 23% odds ratio for kidney disease development in people with the body mass index higher than 30 kg/m^2.

Relation between the obesity surgeries and nephrolithiasis were also noted in other studies. Matlaga B. et al.[14] did a retrospective study in which were analyzed 9278 registers. Of these registers, 50% belonged to non-operated obese patients, and 50% to RYGB operated obese patients. The results showed that the formation of calculi in 7.65% (355) of the 4,639 RYGB patients and in 4.63% (215) of the 4,639 non-operated obese patients, expressing a statistical difference, with higher risk to calculi formation in obese operated patients.

In a retrospective study, Whitson et al.[24] noticed, based on a publication of Durrani O. et al.[8], that there was renal calculus formation *de novo* in only 3.2%. However, in patients with nephrolithiasis history, 31.4% had recurrent calculi after

TABLE 1 - Data extracted from each selected study

Autor	Number of patients(n)	Kind of study	Comparison/kind of surgery	Following period (months)	Nephrolithiasis prevalence	Supporting evidences
Froeder et al., 2012	61	Prospective	RYGB(58) BPD-DS(3)	12 (months)	3 of 61 (4,9%) forming stones de novo after surgery	↑ excretion of CaC2O4 and Citrate
Alexander J et al. 2008	18	Prospective	GB(14)/4(VG)	6 (urine analysis)	NR	No alteration
Nasr et al., 2008	11	Prospective	RYGB(8)/3 Total Gastrectomy (Roux-en- Y esophagojejunostomy)	mean and median follow-up of 19,4 and 11.0 mo, respectively (range 2.5 to 58.0 mo)	Not Mentioned	NR
Patel N et al. 2009	9	Prospective	RYGB (6) Bypass Jejunoileal(2)/BPD- DS(1)	Different kind of study, 7 days with controlled diet	66,67%	Urine volume, pH and citrate, contribuing for cance CaC2O4 supersaturation
Kumar R et al. 2010	58	Prospective	RYGB(52)/BPD-DS(6)	6 (urine analysis)	NR↑	↑ excreção de CaC2O4 BGRY(23%)/BPD-DS (50%))
Matlaga B et al. 2009	11	Prospective	RYGB(9)/BPD-DS(2)	6 e 12 (urine analysis)	NR	↑ eexcretion of CaC2O4
Duffey G et al. 2010	21	Prospective	RYGB	3,12 e 24 (urine analysis)	NR	↑ eexcretion of CaC2O4(52%)
Chen T et al. 2013	417	Retrospective	AGB(332)/VG(85)	54 (search for nephrolithiasis)	AGB (3.4/1000 year) G(5.2/1000-year	NR
Matlaga B et al. 2009	9278	Retrospective	RYGB(4639)/Obesos controle(4639)	60 (at least 36)[search for nephrolithiasis]	RYGB 7,65% = 355/ Obese 4,63% = 215	NR
Whitson et al. 2010 - Review	5|60 - BS	Retrospective	RYGB	Not Mentioned	3,2%	↑ excretion of CaC2O4 and Citrate

NR = Not reported; RYGB = Roux en Y Gastric Bypass; AGB = Adjustable gastric band; VG = Vertical Gastrectomy; BPD-DS = Biliopancreatic diversion with Duodenal Switch; CaC2O4 = Calcium Oxalate

RYGB, due to the progressive rising amount of oxalate after surgery[23].

A hiperoxaluria is a characteristic factor post-bariatric surgery and is maintained even on a restrict oxalate diet in patients submitted to the procedure, in spite of the overall calcium oxalate supersaturation decrement as Pang et al.[20] found in their study. Nelson WK et al.[19] in 2005 already pointed enteric hyperoxaluria, nephropathy and nephrolithiasis caused by oxalate as additional risks for RYGB.

Among the non-operated obese patients, the nephrolithiasis prevalence is greater than in general population, and the composition of the calculi is predominantly uric acid[3]. In this cohort of patients, the obesity itself promotes a biochemical condition that cooperates with the kidney stone formation such as pH reduction, raised excretion of calcium, oxalate, uric acid, and, as remembered by Dardamanis M.[5], the crystalopoesis of a salt does not rely only in its hypersaturation, but in a group of conditions like pH alteration previously mentioned added to the ionic activity of soluble salts, existence of complex salts in the solvent and, finally, the salt concentration above the formation product (region of hypersaturation or instability).

Moreover, it is worth highlighting that the uric acid stones can be aggravated by three factors, such as the reduction of urinary volume, hyperuricosuria and urine's abnormally acidic pH, being the last one the main aggravating of uric acid crystallization. And as mentioned previously, obesity promotes it [5].

Exceptionally, in the obese patients that underwent bariatric surgery, several studies have shown hyperoxaluria as a determining lithogenic factor[3] being it confirmed as the most significant abnormality of modern bariatric surgery[23].

Prevalence of calcium oxalate in that group motivated the accomplishment of studies to clear the involved mechanism of lithogenesis. Evidences have shown that calcium oxalate accumulation may be caused by a already known mechanism (Figure 2) in which happens saponification of the calcium ions with free fat acids in the bowel, leaving more oxalate free in the intestinal lumen for subsequent colon absorption[3].

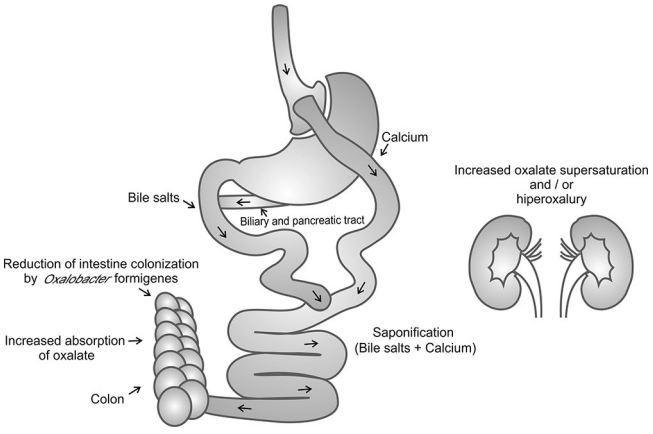

FIGURE 2 - Mechanism of saponification and hyperoxaluria due to RYGB

Regarding the mechanism prior described, Kumar et al.[12] accompanied the urine and feces composition in intervals of six and 12 months of 11 patients who underwent bariatric surgery, being nine RYGB and two biliopancreatic diversion with duodenal switch, and they demonstrated that there was a raise in fecal fat as well as a raise in the oxalate levels after a overloaded ingestion of calcium oxalate. These findings confirmed the calcium saponification mechanism and the increased enteric absorption of oxalate. Without the overload, the oxalury levels din't demonstrate expressive growth.

To explain the oxalury non-augmentation, differently from the preceding paper of his group, Kumar et al.[12], evocate the calcium supplementation of 1,600 mg/day for a year post-surgery. And they justify that the calcium oxalate supersaturation growth as a consequence of the post-surgery reduced urinary volume and increasing of the urinary calcium levels.

Two other prospective studies demonstrated the occurrence of hyperoxaluria in the patients during post-operation period. Duffey et al.[6] analyzed the urine of 21 patients who underwent RYGB in gaps of 3, 12 and 24 months. Patel N. et al.[21] analyzed the urine of 58 patients being 52 RYGB, and six biliopancreatic diversion with duodenal switch, in six month interval post-surgery. Both found hyperoxaluria.

Other mechanism that has been proposed to explain the hyperoxaluria is the probable change in the intestinal flora after the surgery, with the reduction of *Oxalobacter formigenes* colonization in the bowel. This bacterium is naturally present in the intestinal flora, and it is responsible for oxalate degradation. This change contributes to increase oxalate absorption, because, as demonstrated by Kaufman DW et al.[11], patients that present their gastrointestinal tract colonized by that bacterium have 70% less risk in becoming a recurrent calculi former. Also, it is worth remembering that, as patients who undergo surgical procedures are submitted to antibiotic administration, it could be possible that some of these drugs may cause an alteration in this bacterium population. Mainly drugs like macrolides, tetracyclines, chloramphenicol, rifampicin and metronidazole which are harmful to the *Oxalobacter formigenes*[11,7,2].

When was analyzed the restrictive procedures, was found different results regarding oxaluria. Alexander J. et al.[1] analyzed the urine of 18 patients, being 14 gastric band and four of vertical gastrectomy, in a interval of six months post-surgery and they didn't find any changes. One of the reasons for that conclusion, was perhaps the little number of patients that were analyzed in short time after the surgery. Another point to be thought about would be the different kinds of surgery in which the analyzed patients by Alexander J. et al.[1] were submitted. RYGB is considered as a great option to obesity and its comorbidities, but the hyperoxaluria promoted by this procedure is also more severe than in other sorts of surgery like gastric band and vertical gastrectomy[6].

Still considering the restrictive procedures, another aspect became evident in a study of Chen T. et al.[4], in which they analyzed the reports of 417 patients, being 332 adjustable gastric band and 85 vertical gastrectomy, was the finding of stone formation rate of 12.4/1,000/year for patients with adjustable gastric band and a 5.2/1,000/year in vertical gastrectomy. These results indicate that not only the occurrence of surgery is an important condition in the determination of nephrolithiasis prevalence, but also the sort of surgery.

From the mechanism of calculus formation already mentioned, measures have been adopted to attenuate this comorbidity as suggested by Matlaga et al[14]. These measures are: compatible diet with the new condition (bariatric surgery operated patient), increase fluid consumption (average amount around 2,000 ml), reduce sodium, animal protein and foods that may contain oxalate consumption. All of that should be followed by calcium supplementation of 1,200-2,000 mg/day - preferentially in the form of calcium citrate as indicated by Mechanik JI et al[15] -, as far as the restrictive diet alone doesn't provide significant results[20]. This consumption of calcium citrate is necessary since not only the calcium absorption decreases in RYGB patients but also there are large numbers of patients in whom hypocitraturia has been reported[13]. Biochemically, it is known that the citrate binds with the calcium, thus forming a soluble salt and consequently preventing that ion to bind with the oxalate.

The articles highlight that more prospective studies, with

longer follow-up time, that also evaluate the hyperoxaluria, are necessary for more efficient interventions.

Final considerations

There is an increased prevalence of obesity, its comorbidities and consequently, it is expected that more obesity surgeries will be performed. Recent studies show a relationship between obesity surgery and nephrolithiasis even in higher levels than those related only to obesity. More efforts are needed, such as prospective studies with greater population to define the most adequate procedure to achieve weight loss and decrease the risk of potential consequences not yet well considered, such as urinary calculi**.**

CONCLUSION

There is correlation between obesity surgery and nephrolithiasis.

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