

# Other aspects of bariatric surgery: liver steatosis, ferritin and cholesterol metabolism

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## Abstract

Bariatric surgery developed in the late 1970 to treat severe hyperlipidemias in overweight individuals, not necessarily obese. Several techniques have been developed, and the concept has come first of a surgery for morbid obesity, then of a cure for diabetes in morbid obesity. There are other aspects of bariatric surgery that deserve attention, beyond BMI and diabetes, such as hypertension, poor life expectancy, increased prevalence of cancer, congestive heart failure, social inadequacy. The aim of this presentation is to review some recent development in clinical research, in the fields of liver steatosis, ferritin metabolism, and cholesterol metabolism.

Liver steatosis, also called fatty liver encompasses a graduation of diseases with different clinical relevance and prognosis. NAFLD correlates with atherosclerosis, insulin resistance and diabetes mellitus. There is now evidence that weight loss, obtained through diet or restrictive surgery, reduces the prevalence (and the severity) of NAFLD.

An other issue is represented by serum ferritin concentrations, that are strongly associated with fibrosis, portal and lobular inflammation in NAFLD patients, especially in the presence of obesity. Body iron contributes to excess oxidative stress already at non iron overload concentrations. Moreover, serum ferritin is an important and independent predictor of the development of diabetes. Weight loss is accompanied by reduction of ferritin, more after restrictive than malabsorptive surgery.

Metabolic changes are greater after malabsorptive or mixed surgery than after purely restrictive surgery, and this has been ascribed to a greater weight loss. Studies comparing the two kinds of surgery indicate that, for the same amount of weight loss, decrease of cholesterol is greater with the former than with the latter techniques, and this difference is mainly due to a greater reduction of intestinal absorption of cholesterol. In the choice of surgery for the single patient, among other aspects, malabsorptive surgery seems to be more indicated in subjects with hyperlipidemia, especially with high cholesterol levels.

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Key words: *Bariatric surgery. Liver steatosis. Ferritin. Cholesterol metabolism.*

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## OTROS ASPECTOS DE LA CIRUGÍA BARIÁTRICA: ESTEATOSIS HEPÁTICA, METABOLISMO DE FERRITINA Y COLESTEROL

### Resumen

La cirugía bariátrica se desarrolló a finales de la década de los 70 para tratar la hiperlipidemia severa en personas con sobrepeso, no necesariamente obesas. A lo largo de los años se han desarrollado varias técnicas quirúrgicas que han sido utilizadas en primer lugar en la obesidad mórbida y posteriormente en el tratamiento de la diabetes. Hay otros aspectos de la cirugía bariátrica que merecen atención más allá del IMC y la diabetes, como la hipertensión, la pobre esperanza de vida, una mayor prevalencia de cáncer, insuficiencia cardíaca e inadaptación social. El objetivo de este artículo es revisar los recientes avances clínicos en campos de investigación relacionados con la esteatosis hepática, el metabolismo de ferritina y el metabolismo del colesterol.

La esteatosis hepática, también llamada hígado graso abarca una serie de las enfermedades con diferente pronóstico y relevancia clínica. El Hígado Graso No Alcohólico (NAFLD siglas en inglés) se correlaciona con la aterosclerosis, resistencia a la insulina y diabetes mellitus. Hoy en día existen evidencias de que la pérdida de peso que se obtiene a través de la dieta o cirugía restrictiva, reduce la prevalencia (y la gravedad) de la NAFLD.

Otro tema de estudio incluye las concentraciones de ferritina sérica, que están fuertemente asociadas con la fibrosis e inflamación lobular y portal en pacientes con NAFLD, especialmente en presencia de obesidad. El exceso de hierro corporal en obesos contribuye a un aumento del estrés oxidativo debido a una sobrecarga en su concentración. Por otra parte, la ferritina sérica es un indicador importante e independiente del desarrollo de la diabetes. La pérdida de peso se acompaña de una disminución de la ferritina. Esta disminución es más evidente tras una cirugía restrictiva que tras una malabsortiva.

Los cambios metabólicos son mayores después de una cirugía malabsortiva o mixta que tras una cirugía puramente restrictiva, y esto se ha atribuido a una mayor pérdida de peso. Estudios que comparan los dos tipos de cirugía indican que, para la misma pérdida de peso, la disminución de colesterol es mayor con las primeras técnicas que con las últimas, y esta diferencia se debe principalmente a una mayor reducción de la absorción intestinal del colesterol. En la elección de la cirugía para un paciente concreto, entre otros aspectos, la cirugía de malabsorción parece estar más indicada en sujetos con hiperlipemia, especialmente con altos niveles de colesterol.

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Palabras clave: *Cirugía bariátrica. Esteatosis hepática. Ferritina. Metabolismo colesterol.*

## Introduction

Metabolic surgery has been proposed as the new name of bariatric surgery, but was developed in the late 1978 to treat severe hyperlipidemias in above-normal body weight individuals, not necessarily obese; the Program on the Surgical Control of the Hyperlipidemias (POSch) can be considered the beginning of a surgery for morbid obesity, then of a cure for diabetes in morbid obesity. Nevertheless, there are other aspects of bariatric surgery that deserve attention, as raised Body Mass Index BMI and diabetes are not the only co-morbidities of obesity; think of hypertension, poor life expectancy, increased prevalence of cancer, congestive heart failure, social inadequacy. Given the strict links between obesity, chronic sub-clinical inflammation, insulin resistance, diabetes, the metabolic syndrome, and steatosis, the aim of this presentation is to review some recent development in clinical research, basic and surgical.

## Liver steatosis

Liver steatosis, also called fatty liver encompasses a graduation of diseases with different clinical relevance and prognosis; simple NAFLD (non Alcoholic Fatty Liver Disease) is more frequent and less severe than NASH (Non Alcoholic Steato Hepatitis), as the former is a benign condition, the latter can proceed to cirrhosis and probably also to hepatocellular carcinoma.<sup>2</sup>

Prevalence of NAFLD has been defined through biopsies (that is considered the gold standard for the diagnosis, in that a differentiation between steatosis, steatosis plus fibrosis, steatohepatitis is possible), autopsy series, and non-invasive methods such as liver ultrasound, liver enzymes (ALT and AST plus GGT), magnetic resonance imaging (MRI). Though considered the gold standard, biopsies are not suitable for population studies; one would wonder whether it is ethical to perform repeat liver biopsies for research purposes. Expectedly, the prevalence of NAFLD varies in different studies, that is in different populations, and using different criteria and methodologies; in summary, NAFLD (and NASH) affect a significant proportion of adults of both sexes. NAFLD is quite frequent in obesity, in diabetes, in metabolic syndrome, and is expected to increase worldwide due to the obesity epidemics, and is also increased with increasing alcohol consumption.<sup>2,3</sup>

NAFLD correlates with atherosclerosis, insulin resistance and diabetes mellitus,<sup>4,5</sup> whatever the method of assessment of NAFLD. In the large European population (RISC Study) NAFLD, evaluated through the fatty liver index, was associated with increased CHD risk, low-density lipoprotein cholesterol, systolic blood pressure, and intima-media-

thickness, and inversely associated with insulin sensitivity, high-density lipoprotein cholesterol, adiponectin, and physical activity.<sup>4</sup> Based on liver biopsies, about three quarters of bariatric surgery patients have liver steatosis, and about a quarter have fibrosis.<sup>6</sup> There have been attempts to predict frequency and severity of fatty liver based on liver function tests; in 200 patients, multivariate analysis identified six predictive factors for NASH: the diagnosis of HT, DM, sleep apnea, AST > 27 IU/L, ALT > 27 IU/L, and non-black race;<sup>7</sup> however, in 139 patients undergoing bariatric surgery, NASH was found in 57 (41%): age, gender, race, BMI, DM, HT, and liver function tests and triglyceride, cholesterol, iron, and prealbumin measurements were not strong predictors of NASH [8]. Imaging has been proposed as a surrogate of liver biopsies; ultrasound, compared with biopsy, has an accuracy 0.81%;<sup>6</sup> a recent meta-analysis indicates that the diagnostic accuracy is greater for magnetic resonance imaging (MRI), chemical-shift MRI and for spectroscopy-MRI;<sup>9</sup> the two latter techniques correlate, and accurately estimate the severity of steatosis.<sup>10,11</sup> During the last 5 years we have developed a MRI chemical-shift analysis to differentiate NAFLD from other infiltrative liver disorders such as glycogenosis.<sup>12-14</sup> This technique requires simple MRI instruments, correlates with ultrasound, and preliminary data indicate a high frequency of NAFLD in obese subjects, paralleled by frequent elevation of liver enzymes.<sup>15</sup>

The next question is: what is the effect of weight loss on NAFLD? There is now abundant evidence that weight loss, obtained through diet or restrictive surgery, reduces the prevalence (and the degree) of NAFLD; this applies to biopsies, to ultrasound studies, to MRI studies, as well as to liver function tests, and the different criteria seem to yield the same kind of information; also NASH seems to regress to simple NAFLD.<sup>15-20</sup> The drop of AST and ALT correlates with loss of visceral fat.<sup>21</sup> Interestingly, the effect of malabsorptive surgery (biliointestinal bypass) is less clear (liver enzymes),<sup>22</sup> but there is no recent data showing worsening of NAFLD or NASH after bariatric surgery.

## Ferritin

Serum ferritin concentrations and BMI are strongly associated with fibrosis, portal and lobular inflammation in NAFLD patients.<sup>23</sup> Diabetes and metabolic syndrome are the main contributors to high ferritin levels in obesity.<sup>24</sup> Growing evidence has shown that even moderately increased iron stores, represented by high-normal ferritin concentrations, are associated with diabetes.<sup>25-28</sup> More recently the results from prospective studies from Caucasian populations suggested that iron overload could predict the development of abnormal glucose metabolism.<sup>29</sup>

It is unclear whether elevated ferritin may simply be another marker of insulin resistance or whether

elevated ferritin concentrations identify iron stores that may contribute to the pathogenesis of altered metabolic states. A recent study has suggested that body iron contributes to excess oxidative stress already at non iron overload concentrations.<sup>30</sup> Moreover, serum ferritin has been identified as an important and independent predictor of the development of diabetes<sup>31</sup> and high concentrations of ferritin, together with low oral glucose insulin sensitivity, have been identified as independent markers of fibrosis in NASH.<sup>32</sup>

It has been hypothesized that iron could be an important cofactor in the pathogenesis and progression of some cases of NASH<sup>31</sup> since NAFLD subjects have increased hepatic fatty acid oxidation, and increased production of ROS.<sup>30-32</sup> In a large cohort of NASH patients, 21.1% had hyper-ferritinemia while only 7.4% had signs of peripheral iron overload and 9% had signs of hepatic iron overload.<sup>31</sup>

Among other things, weight loss is accompanied by reduction of inflammation, and ferritin is both a storage protein for iron and a marker of inflammation; ferritin decreases after surgery, more after restrictive than malabsorptive surgery.<sup>33-36</sup> Considering the close relationship between obesity, insulin resistance and development of NAFLD, we studied their association with hepatic profile and ferritin concentrations.<sup>34</sup> Since bariatric surgery-weight loss is associated with reduced insulin resistance, restored glucose tolerance, reduced hepatic steatosis, and improved liver enzymes, we repeated the analyses after laparoscopic gastric banding surgery to evaluate the impact of weight loss on the association between hepatic profile, ferritin concentrations, and insulin resistance. In our group of 169 obese subjects (89 with normal liver enzymes, 70 with raised liver enzymes), before bariatric surgery, ferritin concentrations were increased proportionally to ALT concentrations, although, in general, within normal ranges and similar in NGT, IGT, and T2DM. A positive correlation was observed between ferritin plasma concentrations and insulin resistance. After surgery, however, we did not observe a significant decrease in plasma ferritin concentrations despite the improvement in hepatic function and insulin resistance. However, the correlations between ferritin, ALT, and insulin resistance remained suggesting that ferritin may simply identify a new phenotype of insulin resistance.<sup>34</sup>

### Cholesterol metabolism

Metabolic changes are greater after malabsorptive or mixed surgery (bilio-pancreatic diversion, gastric by-pass) than after purely restrictive surgery (vertical banded gastroplasty, gastric banding, intra-gastric balloon), and this has been ascribed to a greater weight loss; no surprise that disappearance of comorbidities like diabetes mellitus happens more frequently after the former than after the latter interventions.<sup>37</sup> Even though improvement of hyperlipidemia was present in a fair

proportion of subjects undergoing gastric banding (triglycerides 78%, 94%, 87%; cholesterol 77%, 91%, 100% with gastric banding, gastric bypass, and bilio-pancreatic diversion, respectively, the degree of reduction of cholesterol levels was clearly different (-0.30, 0.96, 1.97 mmol, respectively). We reported decreased cholesterol levels after bilio-intestinal by-pass (an other malabsorptive surgery)<sup>22</sup> or after bilio-pancreatic diversion,<sup>38</sup> but not after gastric banding. The cholesterol reduction that we and others have reported after after bilio-intestinal by-pass, bilio-pancreatic diversion, or gastric by-pass is a quite dramatic phenomenon and is likely due to the major reduction in bile acid re-absorption in the intestine, and possibly to altered regulation of the feedback mechanisms controlled by nuclear protein such as LXR, FXR and PPAR; these transcriptional factors are involved in bile acid and cholesterol metabolism, occurring in patients undergoing after bilio-intestinal by-pass, bilio-pancreatic diversion or gastric by-pass (which cause malabsorption and also reduced bile re-absorption), but not gastric banding (a purely restrictive bariatric procedure).<sup>39</sup> It is also possible that reduced gastric volume and reduced production of gastric lipase, as well as reduced secretion of cholecystokinin (that physiologically stimulates digestive enzyme secretion such as lipases and proteases) might result in a marked decrease in the hydrolysis of triacylglycerols, with a reduction of the absorption of free fatty acids.<sup>40</sup> Both bilio-pancreatic diversion and gastric by-pass include partial gastric resection, or functional gastric disconnection; therefore, gastric by-pass and bilio-pancreatic diversion can not be regarded as purely restrictive or purely malabsorptive surgical techniques. We hypothesized that, aside from greater weight loss, a specific effect of malabsorptive surgery on cholesterol metabolism might exist, probably mediated by intestinal milieu.<sup>41,42</sup> We also observed that, at six months, weight loss was similar with gastric banding and with bilio-intestinal by-pass.<sup>22</sup> Therefore we performed a comparison of gastric banding, intra-gastric balloon, and bilio-intestinal by-pass, and hypocaloric diet (1,200 kcal/day), on glucose and cholesterol levels in morbid obesity. We could confirm that, at 6 months, weight loss is similar with the three surgical techniques, greater than with diet, and that glucose metabolism was also similarly affected; however, serum cholesterol and LDL-cholesterol levels were affected in a significant way only by bilio-intestinal by-pass.<sup>43</sup> Then we evaluated intestinal cholesterol absorption, endogenous cholesterol synthesis, and cholesterol catabolism through the bile acids pathway, and we found that after bilio-intestinal by-pass, together with decreased cholesterol levels, intestinal cholesterol absorption is reduced, associated with enhanced cholesterol synthesis and enhanced cholesterol catabolism; in contrast, after gastric banding there is no change in cholesterol levels, in cholesterol absorption, synthesis, and only a marginal increase in cholesterol catabolism.<sup>44</sup>

## Conclusion

Decision on which surgical procedure to choose for the individual obese patients is a complex matter, that has to take into consideration expectations, invasiveness and reversibility, surgical mortality, drawbacks of each surgical procedure,<sup>45,46</sup> among other aspects, malabsorptive surgery seems to be more indicated in subjects with hyperlipidemia, especially with high cholesterol levels.

## Declaration

The authors have no conflict of interests with the contents of this paper.

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