

# Endometrial cancer prevention - does bariatric surgery play a role?

## Abstract

Once obesity became a global health problem, the incidence of various malignancies reported a significant increase, leading to the hypothesis that a certain correlation might exist. This correlation was evident especially in hormonally dependent tumors such as endometrial cancer and breast cancer. In consequence, attention was focused on determining whether bariatric surgery weight loss induction might play a protective role.

**Keywords:** endometrial cancer, obesity, bariatric surgery

## Introduction

Endometrial cancer is one of the most commonly encountered in women worldwide, with increasing incidence in overweight and obese patients. It has been widely recognized that weight excess as well as diabetes mellitus, arterial hypertension and dyslipidemia are frequently present in these cases<sup>(1,2)</sup>. Other situations which were positively associated with endometrial cancer include early age at menarche, late menopausal onset, tamoxifen therapy, nulliparity and the presence of endometrial lesions such as complex endometrial hyperplasia or endometrial polyps<sup>(3,4)</sup>. Among all these risk factors, obesity and its' related comorbidities (i.e. diabetes mellitus, arterial hypertension, dyslipidemia) are the most easily to be controlled factors, both excess weight and associated comorbidities being significantly easier to be controlled once the weight loss process is induced. As far as this process is concerned, it can be induced both by conservative or surgical procedure. Although conservative methods seem to have good results on short term periods, it seems that when it comes to the long term follow up, almost all patients experience weight regain. Surgical procedures, known under the general name of bariatric surgery are capable to induce a long term, durable weight loss and good control of the associated comorbidities<sup>(5-9)</sup>. The largest study conducted on the benefits of bariatric surgery on obese patients was the SOS study which was conducted on Swedish obese patients and showed the superiority of bariatric surgery when compared to the conservative weight loss methods. Although cancer prevention was not a primary end point of the study, the authors reported a decreased incidence of cancers among obese women submitted to bariatric compared to their counterparts submitted to conservative weight loss methods. Surprisingly, this effect failed to be demonstrated in obese men, and sustained the idea that one of the principals incriminated mechanisms in cancer reduction incidence is a hormonal related one<sup>(10)</sup>.

## Histopathological subtypes of endometrial cancer

According to Bookman's classification, endometrial cancer is mainly classified in two histopathological types, with different biological features and different long term outcomes. Type one endometrial tumors include low grade, well differentiated endometroid adenocarcinomas which grow slowly, under a strong hormonal influence. However, they express multiple hormonal receptors and have overall a good prognosis with high rates of 5-year survival rates. These tumors represent up to 85% of all endometrial cancers, are usually diagnosed in early of the International Federation of Gynecology and Obstetrics stages, have favorable tumor biology and are responsible for a small number of endometrial cancer related deaths. They are usually present in obese, diabetic, postmenopausal women. Type two endometrial cancers are responsible for only 15% of all endometrial cancers, are biologically aggressive tumors and are responsible for the majority of endometrial cancer related deaths<sup>(11)</sup>. The main histopathological subtypes include clear cell and serous endometrial carcinomas, as well as poorly differentiated endometroid adenocarcinomas. Most often patients diagnosed with this histopathological subtype are younger, normal weighted patients and have a significantly poorer outcome<sup>(12)</sup>. They are usually diagnosed in more advanced stages and the overall survival is significantly lowered in comparison with type I tumors. In the meantime, the hormonal dependence of these tumors seems to be lower<sup>(11,12)</sup>.

## The connection between endometrial cancer and obesity

Obesity is associated with multiple metabolic modifications on various lines, inducing endometrial malignant transformation via multiple mechanisms. The main incriminated routes include estrogen excess, modified glycemic homeostasis, increased insulin levels and increased insulin

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resistance as well as the chronic pro-inflammatory status which is associated with high levels of adipokines<sup>(13-20)</sup>.

1. It is well known that adipose tissue has a high capacity of estrogen synthesis, being associated with higher aromatase activity levels, leading throughout this mechanism to the apparition of higher estrogen circulating levels. In obese postmenopausal women, when ovarian estrogen secretion decreases, the adipose tissue remains the principal organ responsive for this hormonal excess. The estrogen excess will have a positive effect of the mitogenic and anti-apoptotic activity, inducing a carcinogenic effect. Moreover, obesity was associated with higher androgen levels which also seem to have a mitogenic and anti-apoptotic effect<sup>(13,16-18)</sup>.

2. Obesity was also associated with high levels of circulating glucose, inducing the frequent association of diabetes. As a compensatory mechanism, pancreatic cells will be stimulated to secrete a higher amount of insulin, inducing in this way a chronic hyperinsulinemic status. This status will persist for a long period of time, until the moment in which a pancreatic depletion will occur. In this case the pancreatic islets will be no longer capable of secretion, this status being revealed by lowering levels of C peptide. It is well known that, apart from its' function in glucose metabolism regulation, insulin also acts as a growth factor, inducing cellular proliferation. In all this period, the chronic hyperinsulinemia will have a mitogenic effect on the endometrial cells inducing endometrial malignant transformation. Furthermore, obese patients also reported a higher insulin growth factor level which also has a mitogenic and anti-apoptotic effect of the endometrial lining<sup>(19,20)</sup>.

3. Obesity was also associated with a pro-inflammatory status, being associated with high levels of interleukines, tumor necrosis factors and adipokines. The most cited adipokines in endometrial malignisation are leptin and adiponectin. Obesity was also associated with higher leptin levels and, consequently with a mitogenic and anti-apoptotic effect of the endometrial lining. In the meantime, adiponectin, an adipokine with protective effect against malignant transformation, is present in lower amounts in obese patients, increasing in this way the risk of endometrial cancer development<sup>(14,15,18)</sup>.

### The effect of bariatric surgery on obese postmenopausal women at risk to develop endometrial malignization

Bariatric surgery has become in the last decades the golden standard in treating morbidly obese patients and in the amelioration of obesity related comorbidities. Bariatric surgery mainly comprises restrictive and malabsorptive procedures. Restrictive bariatric procedures induce a significant decrease in the amount of ingested food, the most commonly performed procedures including adjustable gastric banding and sleeve gastrectomy. Adjustable gastric banding consists in placing a silicon band in the proximity of the cardia which is connected to a subcutaneous port. The band comes to create two gastric pouches, a little one at the superior part of the stomach, which becomes the

utile one and the remnant, larger part of the stomach. The band will create a narrowing at the site where it is placed, impeding the patients to eat a higher amount of food than the volume of the small pouch situated in its upper part. Although initially was used with good results, it has been showed that weight regain as well as mechanical complications due to the intra-gastric slippage of the band are common. Therefore, the method is rarely used nowadays, remaining the treatment of choice for patients who desire only a limited weight loss<sup>(21)</sup>. In this case, patients can easily learn how to bypass the effect of the band, by consuming high caloric liquids, ice cream, juices, which can easily pass through the band without inducing the satiety sensation; in consequence the patient will have a permanent hunger sensation and will experience a higher amount of calories intake, leading to weight gain. Laparoscopic sleeve gastrectomy is another bariatric surgical procedure which induces a restriction of the food intake. It has a higher success rates, and a lower rate of long term complications or weight regain. It consists in longitudinal sectioning the stomach of the pylorus to the cardia by using the stapling devices, creating in this way a narrow gastric tube<sup>(22)</sup>. Although during the postoperative period there is a certain risk of postoperative complications such as bleeding or gastric leaks, the rate of such complications significantly dropped down in the last years, transforming laparoscopic longitudinal gastrectomy into the most commonly performed bariatric surgery procedure in Europe. It induces a constant and sustained weight loss, with low rates of weight regain at 5-year follow up and, in the meantime with low rates of metabolic deficiencies. However, sustained administration of vitamins and supplements during the first postoperative months is recommended in order to avoid nutritional deficiencies<sup>(23)</sup>.

Malabsorptive procedures represent another subcategory of bariatric procedure which consists in bypassing a significant length of the digestive tube in order to decrease the amount of nutrients which reach the patients' circulation. While all types of malabsorptive surgical procedures induce bypassing of a certain length of the small bowel, other procedures also provide gastric bypassing, increasing the malabsorptive effect. The most commonly performed malabsorptive procedures include Roux en Y gastric bypass and loop gastric bypass. These procedures consist in creating a small gastric pouch at the superior gastric pole by using the stapling devices, which will be connected throughout an anastomosis to a small bowel loop. The distance from the duodeno-jejunal angle at which this anastomosis will be performed will establish the malabsorption rates. As the distance between the duodeno-jejunal angle to the anastomosis increases, the malabsorptive effect also increases, and a higher length of small bowel being bypassed. The type of bypass performed (i.e. loop or Roux en Y), depends on the established circuit. If a single, gastro-jejunal anastomosis is performed, on a continuous small bowel loop, the procedure will be called loop gastric bypass. If the anastomosed enteral loop will be then interrupted and re-implanted in the

distal jejunal loop, the procedure will be transformed in Roux-en Y gastric bypass. Other malabsorptive procedures include bilio-pancreatic diversion and duodenal switch, which are rarely recommended due to the important and sometimes debilitating malabsorptive effect<sup>(24)</sup>. The rate of early postoperative complications in malabsorptive procedures is low, the most commonly reported being bleedings and leaks while during the late postoperative period internal hernias and intestinal obstructions might be encountered. Due to the induced malabsorptive effect, these procedures might be associated with high rates of hypoglycemia and dumping syndrome. In the meantime, the induced depleting effect on the nutrients' deposits necessitates a long-term, sustained program of vitamins and minerals administration<sup>(24,25)</sup>.

However, all these procedures primarily induce weight loss, followed by decreasing the adipose mass and, secondarily, the estrogen and androgen secretion, decreasing the glycemic levels and improves the glycemic control, decreasing the insulin circulating levels, and inducing a decreased pro-inflammatory status. By modulating all

these mechanisms, it significantly decreases the type one endometrial cancer risk<sup>(26)</sup>. Moreover, it has been showed that bariatric surgery seems to improve the outcomes of endometrial cancer survivors. This fact is mainly explained by reducing the excess of weight and amelioration of the associated comorbidities; studies have shown that obese endometrial cancer survivors are more likely to die due to their excess of weight and due to the associated comorbidities rather than due to the continuation of the malignant process<sup>(27,28)</sup>.

## Conclusions

The relationship between obesity and endometrial cancer is a complex, well recognized one, especially for type I endometrial tumors. Bariatric surgery seems to modulate all the mechanisms throughout which obesity induces endometrial lining malignization, inducing in this way a protective effect. In the meantime, amelioration of obesity's associated comorbidities increases the quality of life and decreases the risk of death even in cases that had been already diagnosed and treated for this malignancy. ■

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