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COMMENTARY

From obesity to uterine fibroids: an intricate network

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Uterine fibroids (UFs) are benign monoclonal tumors consisting of smooth muscle cells and connective tissue that develop within the uterine wall. Also known as uterine leiomyomas, UFs represent one of the most common pelvic tumors, affecting over 70% of women by the onset of menopause, and are one of the leading causes for hysterectomy in the US[1]. Leiomyomas could be completely asymptomatic, but at the same time are a major cause of hospitalization. Annually, among women aged 15–54, UFs-related treatments account for 42 per 10,000 hospitalizations, and in most of the cases the hospital stay is accompanied by some type of surgical procedure (hysterectomy, myomectomy)[2]. Indeed, UFs may be responsible for a wide range of severe and chronic symptoms (heavy menstrual bleeding, anemia, pelvic pressure, bladder/bowel dysfunction, pelvic non-cyclic pain, dyspareunia, infertility, pregnancy complications)[3] with a deep impact on patients quality-of-life[4]. Many risk factors have been identified, including black race, positive family history for UFs, genetic predisposition, use of oral contraceptives or intrauterine devices, nulliparity, early menarche, lifestyle factors, and, recently, obesity[3]. The exact proportion of obese patients undergoing surgical procedures for UFs varies among studies[5,6]. In a study mainly focused on feasibility and outcome of laparoscopy, the percentage of overweight/obese patients who underwent surgery for UFs (myomectomy/hysterectomy) was 24%[6].

Although the etiology is largely unknown, leiomyomas are estrogen- and progesterone-dependent tumors characterized by an increased and disorganized proliferation of smooth muscle cells with an over-production of extracellular matrix (ECM). UFs seem to have an increased sensitivity to sex steroid hormones which is associated with a higher expression of estrogen receptor-α (ER-α) and progesterone receptor (PR) when compared to the normal myometrium[3]. Furthermore, in the luteal phase while normal myometrial cells become quiescent, UFs tissue shows an increase in estrogen-regulated genes, which promotes cell proliferation[7] and grows in response to progesterone (which typically has a suppressive effect on the myometrium)[8].

Recently, a possible correlation with obesity has been taken into consideration, but definitive conclusions have not been drawn. Obesity is chronic disease that nowadays represents a significant global burden of disability and a major public health concern. Several mechanisms may promote the development of UFs in pre-menopausal women with excessive body fat:

i. *Altered sex hormones metabolism*: it is well known that adipose tissue is a dynamic endocrine organ which is responsible for the peripheral conversion of circulating androgens to estrone. Consequently, an increase in the total percentage of body fat may result in an over-production of estrogens, stimulating UFs cells proliferation[9].
ii. *Decreased production of sex hormone binding globulin (SHGB)*: overweight women are more likely to have a reduced hepatic production of SHGB, resulting in more unbound circulating estrogens levels[10].
iii. *Systemic inflammation*: excessive fat accumulation is associated with an increased production of adipokines and inflammatory cytokines that could lead to increased levels of reactive oxygen species (ROS). ROS are able to promote cell proliferation, to inhibit cell apoptosis, and to favor ECM deposition, which represent key events in the onset of UFs[11]. In addition, *in vitro* studies have shown that UFs cells have a defective antioxidant enzymatic activity with a reduced expression of catalase and superoxide dismutase, thus extending ROS effects on smooth muscle cells[12].

Definitive conclusions concerning the possible correlation between obesity and UFs are lacking. Several studies have been published on the topic with conflicting results. Some authors found a positive correlation[13–17] or an inverse J-shaped correlation[18–21], while others reported no association[22–24]. A possible explanation for the inverse J-shaped association may be related to the fact that highly obese women are more likely to have lower levels of sex hormones due to anovulation and reduced menstrual cycling, which are often reported in this kind of patient. Consequently, excessively obese women may have an estrogen deficiency that could explain why the curve initially rises and then steeply falls[21]. A recent study published by Vignini *et al.*[25]

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found a significant positive correlation between preperitoneal fat thickness (PFT) and UFs. The authors' choice to evaluate patients' PFT instead of body mass index (BMI) or WHR (waist-hip ratio) relies on the assumption that visceral fat accumulation rather than obesity itself could be considered a risk factor for diabetes mellitus, cardiovascular diseases, and several types of neoplasms, including uterine cancer. Indeed, visceral fat has been recognized to be a highly active endocrine organ, responsible for the production of several proinflammatory cytokines that lead to chronic inflammation and increased oxidative stress, which play a key role in UFs pathogenesis.

Reduced physical activity, diet, and weight change may also be considered modifiable risk factors for UFs. An inverse association between exercise and risk of UFs has been reported. Indeed, a regular physical activity is responsible for increased SHGB levels and reduced insulin and sex hormones levels. Furthermore, a diet rich in fruit, green vegetables, and fish seems also to play a protective role for leiomyomas[26]. Only a few studies have investigated the relationship between body size and weight change during adulthood and risk of UFs. In the study conducted by Terry *et al.*[20], no association was found between body size in childhood/adolescence and risk of UFs. Similar results have been reported in a recent study: data presented by Lee *et al.*[27] demonstrate that weight gain in adulthood (from the age of 18), rather than current BMI and body size, is associated with a higher risk of developing leiomyomas.

In addition, central obesity in particular is also a component of metabolic syndrome (MetS), which is characterized according to the American Heart Association-International Diabetes Federation definition, by the presence of at least three of the following components (which are all in certain ways correlated to UFs)[28]:

1. Central obesity
2. Hyperglycemia
3. High blood pressure
4. Hypertriglyceridemia
5. Reduced high density lipoprotein cholesterol (HDL-C).

The insulin resistance (IR) following the hyperglycemic status is a frequent finding in patients affected by MetS, and the hyperinsulinemia induced by IR may provide a possible biological link underlying the relationship between UFs and MetS. Indeed, it seems that insulin has a specific direct action on the ovaries. Through insulin receptors or insulin-like growth factor-1 receptors, insulin may promote ovarian hormones secretion and it may also be able to reduce their association with globulins, finally increasing the total level of unbound circulating sex steroid hormones[29]. Furthermore, insulin has been observed to enhance vascular smooth cell proliferation and mitosis (animal models) and to promote UFs' cell growth (*in vitro* studies) by altering the tyrosin kinase signal pathway[29]. However, the association between UFs and IR is still debated, given the conflicting results reported in different experimental studies[30,31].

The possible relationship between hypertension (HTN) and UFs may lie in a common pathogenesis. Some authors have hypothesized that the same vasoactive peptides (e.g. transforming growth factor-β) that stimulate smooth muscle proliferation and vascular remodeling in HTN-induced atherosclerotic lesions may also exert the same action on uterine smooth muscle cells, thus promoting the onset of UFs. On the other hand, it has also been suggested that HTN may be a consequence of UFs following the uterine secretion of angiotensinogenase and the urinary tract obstruction caused by the enlarged uterus[32].

Regarding the association between dyslipidemia and UFs, it is well established that estrogens influence several aspects of lipid metabolism (e.g. HDL-C and triglycerides levels, expression of lipoprotein lipase)[33]. Given the fact that UFs are estrogen-dependent tumors, it seems plausible to hypothesize a relationship between leiomyomas and the development of metabolic diseases. However, reports on this issue disagree[34,35], and further research is required.

In conclusion, the link between obesity and UFs seems plausible, but further investigation is required to elucidate biology and natural history of leiomyomas in order to identify modifiable risk factors and to define effective prevention and management strategies.

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