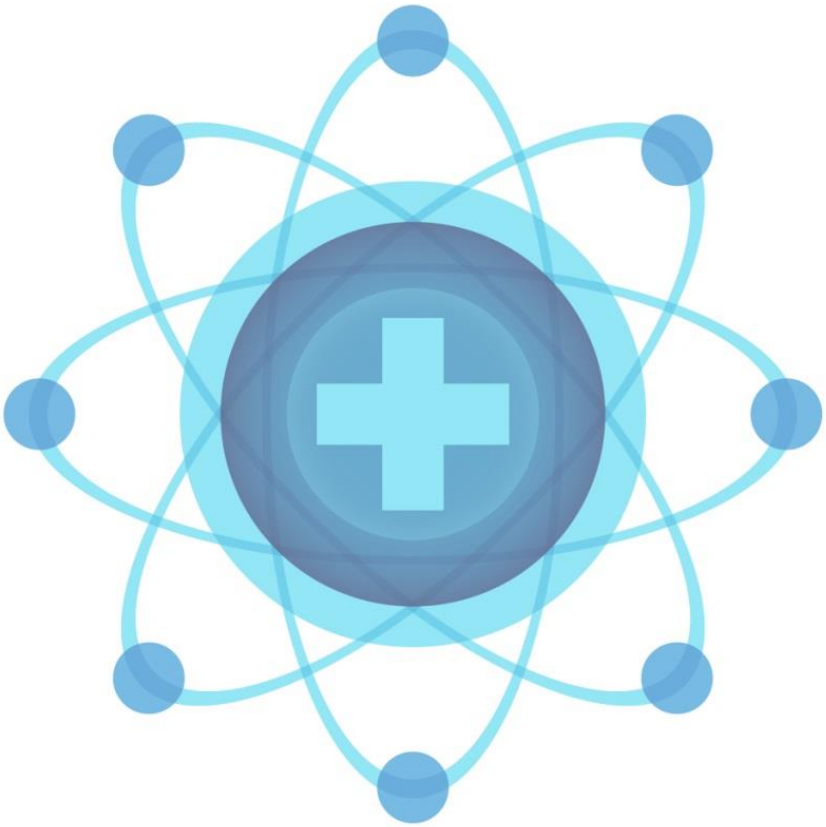

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Obesity and uterine fibroids

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Abstract: The review is devoted to the role of metabolic syndrome in the development of good-quality hyperplastic myometrial lesion. Obesity is a potent potentiating endocrine factor in uterine diseases. Modern correction of endocrine-metabolic disorders is a key component of complex treatment and prevention of hyperplastic diseases of the uterus.

Keywords: uterine fibroids; dyslipidemia; metabolic endocrine diseases; metabolic syndrome

Uterine fibroids (UF) is a benign monoclonal tumor made up of smooth muscle cells and connective tissue that develops in the wall of the uterus. Also known as uterine leiomyoma, UF is one of the most coUFon pelvic tumors, affecting over 70% of women of reproductive and premenopausal age [1]. Leiomyoma can be asymptomatic, but at the same time it is the main reason for hospitalization. Because most patients with UFs remain asymptomatic, the actual incidence of UFs is assumed to be much higher than that reported. Based on the ultrasound screening, the incidence for UFs is reported to be 1.278% in Asia and 3.745% in African- American women per year [2]. 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, such as a positive family history for UFs, combined oral contraceptive use or the use of an intrauterine device, low parity, early onset of menarche, unhealthy lifestyle and, more recently, obesity [3]. 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).

A study showed that obesity leads to changes in endocrine system function, affects the levels of blood sex hormones and alters the secrete modes and metabolic pathways of hormones and their roles in target organs [5]. Furthermore, some current studies have proved that obesity is one of the risk factors for uterine fibroids.

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However, studies on the risk of uterine fibroids in women with central obesity, especially those with relatively large visceral fat area (VFA), are rare.

Obesity is able to cause metabolic disorders, making local tissues to form an abnormally high estrogen environment. The mechanism includes: 1) androstenedione secreted by adrenal glands can be converted into estrone by aromatase in adipose tissues, and the level of estrone in plasma is increased with elevated adipose tissues and strengthened conversion ability, thus leading to persistent estrogen effect; 2) obesity leads to the lack of periodic regulation of progesterone, so that the endometrium is in an environment of over stimulation from no estrogen antagonistic progesterone for a long time [6,7] 3. Systemic inflaUFation: Excessive fat accumulation is associated with increased production of adipokines and inflaUFatory cytokines, which can lead to increased levels of reactive oxygen species (ROS). ROS are capable of stimulating cell proliferation, inhibiting cell apoptosis, and promoting the deposition of ECM, which is a key event in the emergence of UF [8]. In addition, in vitro studies have shown that UF cells have defective antioxidant enzymatic activity with reduced expression of catalase and superoxide dismutase, thus increasing the effect of ROS on smooth muscle cells [9]. 4. Decreased production of sex hormone binding globulin (SHBG): Overweight women are more likely to have decreased production of SHBG by the liver, resulting in more unbound levels of circulating estrogen [10]. Low SHBG concentration has been shown to be associated with increased insulin resistance [11,12]

There are no definitive conclusions about a possible correlation between obesity and UF. Several studies have been published on this topic with conflicting results. Some authors found a positive correlation [13-15] or inverse correlation [16-18], while others reported no association [19-21]. A possible explanation for the inverse correlation may be related to the fact that women with high obesity have lower levels of sex hormones due to anovulation and a decrease in the number of menstrual cycles, which are often observed in such patients.

Decreased physical activity, diet and weight changes can also be considered modifiable risk factors for UF. Feedback has been reported between exercise and UF risk. Indeed, regular physical activity is responsible for increasing SHBG levels and lowering insulin and sex hormones. In addition, a diet rich in fruits, green vegetables, and fish also appears to play a protective role against leiomyomas [22]. Only a few studies have examined the relationship between weight change in adulthood and the risk of UF. A study by Terry et al. [19] found no association between childhood / adolescence weight and risk of UF. Similar results were obtained in a recent study: data presented by Lee et al. [23] show that weight gain in adulthood (starting at age

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18), rather than current BMI, is associated with a higher risk of developing leiomyomas.

Insulin resistance (IR) following hyperglycemic status is coUFon in patients with metabolic syndrome, and hyperinsulinemia caused by IR may provide a possible biological link underlying the relationship between UF and metabolic syndrome. Indeed, insulin appears to have a direct, specific effect on the ovaries. Through insulin receptors or insulin-like growth factor-1 receptors, insulin can promote the secretion of ovarian hormones and can also reduce their binding to globulins, ultimately increasing the total level of unbound circulating sex steroid hormones [24].

In addition, insulin has been observed to enhance the proliferation and mitosis of vascular smooth cells (animal model) and promote the growth of UF cells (in vitro studies) by altering the tyrosine kinase signaling pathway [24]. However, the relationship between UF and IR is still debated, given the conflicting results obtained in various experimental studies [25-26].

Regarding the relationship between dyslipidemia and UF, it is well known that estrogens affect several aspects of lipid metabolism (HDL and triglyceride levels, lipoprotein lipase expression) [27]. Given the fact that UF are estrogen-dependent tumors, it seems plausible to hypothesize a link between leiomyomas and the development of metabolic diseases. However, reports on this issue differ [28,29], and further research is required.

In conclusion, obesity is one of the risk factors for uterine fibroids, and increased body fat (especially abdominal visceral fat) is capable of raising the risk of uterine fibroids. Meanwhile, providing nutrition guidance and changing diet and exercise habits are important measures to prevent the development of uterine fibroids. Further research is needed to elucidate the biology and natural history of leiomyomas in order to identify modifiable risk factors and to identify effective prevention and treatment strategies.

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