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OBESITY AS A RISK FACTOR FOR ENDOMETRIAL PATHOLOGICAL CHANGES

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Abstract

According to the World Health Organization, overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. A body mass index (BMI) over 25 is considered overweight, and over 30 is obese. The elevated BMI is a major risk factor for cardiovascular diseases, diabetes, osteoarthritis, some cancers (endometrial, breast, ovarian, prostate, liver, gallbladder, kidney and colon).

The most common cause of endometrial hyperplasia is high level of estrogens, combined with insufficient levels of progesterone, which causes secretory changes in the proliferated endometrium from estrogens. This excess endogenous estrogen stimulation can stimulate endometrial proliferation resulting in endometrial hyperplasia and endometrial cancer.

The study included a total of 160 respondents. The study group consisted of 120 patients who underwent fractionated explorative curettage due to a medical indication. They were divided into two subgroups: perimenopausal and postmenopausal. The control group consisted of 40 healthy women without fractionated explorative curettage. Anamnestic data were taken from all respondents. Body weight, height and waist circumference were measured in all of the participants. We divided the patients with fractionated explorative curettage into 2 subgroups: with functional and organic changes of the endometrium.

Patients with explorative curettage had a significantly higher BMI and waist circumference than healthy women. Postmenopausal women had a significantly higher BMI and waist circumference than perimenopausal women. Patients with organic endometrial changes had a significantly higher BMI and waist circumference compared to those with functional changes.

***Keywords*:** obesity, endometrial, explorative curettage.

Introduction

According to the World Health Organization, overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. A body mass index (BMI) over 25 is considered overweight, and over 30 is obese. The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. The elevated BMI is a major risk factor for noncommunicable diseases such as: cardiovascular diseases, diabetes, osteoarthritis, some cancers (endometrial, breast, ovarian, prostate, liver, gallbladder, kidney and colon) [1].

The most common cause of endometrial hyperplasia is high level of estrogens, combined with insufficient levels of progesterone, which causes secretory changes in the proliferated endometrium from estrogens. This may occur in patients with obesity, polycystic ovary syndrome, estrogen-producing tumors

(eg granulosa cell tumor), taking estrogen hormone replacement therapy [2]. Endometrial proliferation is a normal part of the menstrual cycle and occurs during the follicular estrogen-dominant phase of the cycle. When the endometrium is exposed to continuous stimulation with endogenous or exogenous estrogen, in the absence of progesterone, endometrial proliferation can progress to endometrial hyperplasia [3]. In obese women, excess adipose tissue results in increased peripheral conversion of androgens (androstendione and testosterone) to estrogens (estrone and estradiol) by the aromatase enzyme in adipocytes. This excess endogenous estrogen stimulation can stimulate endometrial proliferation resulting in endometrial hyperplasia and endometrial cancer [3].

In menopausal women there are increased circulating levels of estrone which leads to development and growth of endometrial polyps [4].

Most endometrial polyps are benign. In a meta-analysis of their malignant potential, the risk was found to be highest in postmenopausal women with vaginal bleeding (2.3%) [5].

In postmenopausal women, estrogen receptors are more prevalent in polyps than in the surrounding normal endometrium [6].

According to American Heart Association, abdominal obesity is defined as waist circumference > 88cm (for women) and > 102 cm (for men) [7]. Waist circumference is a determinant of the amount of abdominal fat. In abdominal obesity, the activity of the aromatase enzyme is increased, the amount of SHBG is decreased and this leads to an increase in free estrogen levels [8]. The proliferation of endometrial glandular cells is stimulated by estrogen [9]. In postmenopausal women, although most patients showed relatively-low estradiol concentrations, the average serum estradiol levels in patients with endometrial cancer were slightly higher than those of healthy control women. These results indicate that cumulative exposure of estrogen for long period has a critical role in endometrial carcinogenesis [10].

Objectives

1. To determine the association of histopathological changes of the endometrium that occur during the period of perimenopause and postmenopause with the body mass index, waist circumference and the level of obesity.
2. To determine the prevalence of functional and organic changes of the endometrium and their association with the body mass index, waist circumference and the level of obesity.
3. To determine the association of the menopausal status with the body mass index, waist circumference and the level of obesity.

Material and Methods

The study was performed at the Specialized Hospital for Gynecology and Obstetrics "Mother Teresa" – Skopje and involved a total of 160 respondents. The study group consisted of 120 patients who underwent fractionated explorative curettage due to a medical indication (abnormal bleeding or ultrasound-diagnosed endometrial abnormality).

They were divided into two subgroups: perimenopausal and postmenopausal. Fractionated explorative curettage was performed under general intravenous anesthesia.

The material (from endocervix and endometrium) in 2 vials with 10% formalin was sent to histopathological analysis to the Institute of Pathological Anatomy at the Medical Faculty - Skopje. The control group consisted of 40 healthy women without fractionated explorative curettage.

We divided the patients with fractionated explorative curettage into 2 subgroups: with functional changes of the endometrium (prolonged and inadequate estrogenic action, deficient secretory phase, endometrial atrophy) and organic changes (endometrial polyp, endometrial hyperplasia without atypia, endometrial adenocarcinoma).

Anamnestic data were taken from all respondents. Body weight, height and waist circumference were measured in all of the participants.

We calculated the Body Mass Index (BMI) with the formula: BMI = body weight (kg) / body height (m^2). Level of obesity was classified according to WHO Classification of overweight in adults according to BMI [11]:

- Malnutrition: < 18.5
- Normal weight: 18.5-24.9
- Overweight: 25-29.9
- Obesity (obesity class I): 30-34.9
- Severe obesity (obesity class II): 35-39.9
- Extreme obesity (obesity class III): >40

Results

Half of the patients (60) were perimenopausal and the other 60 were postmenopausal. The prevalence of functional disorders was 30% (36 patients) and organic changes 70% (84 patients). The most common pathological change of the endometrium was an endometrial polyp (EP) and it was present in 45% of the respondents. Endometrial hyperplasia without atypia (EH) was present in 23.3% of perimenopausal and 15% of postmenopausal women. Endometrial adenocarcinoma (EC) was present in 3% of perimenopausal and 5% of postmenopausal women.

The average BMI had a value of 30.0 ± 4.5 in the group of patients who underwent explorative curettage (study group), and 25.5 ± 3.4 in the group of patients without this intervention (control group). The difference of 4.5 was confirmed as statistically significant ($p<0.0001$).

According to the BMI, normal body weight was measured less often in study group – in 13 (10.8%) vs 17 (42.5%) patients. These patients were less often overweight than those of the control group- 47 (39.2%) vs 18 (45%), and more often with moderate obesity - 40 (33.3%) vs 5 (12.5%). Severe and extreme obesity were registered only in the study group – 16 (13.3%) and 4 (3.3%), respectively. The described differences in the distribution of patients with normal weight, overweight, moderate, severe and extreme obesity between the study and control groups were statistically significant ($p<0.0001$) [table 1].

Patients of the study group had a significantly larger waist circumference compared to patients of the control group (96.1 ± 11.4 vs 83.3 ± 9.9 cm, $p<0.0001$) [table 1].

Table 1. Distribution according to BMI and waist circumference

variable	**groups**			**p-level**
	n	**Study group**	**Control group**	
BMI (kg/m^2)				
mean ±SD	30.0 ± 4.5		25.5± 3.4	t=5.8
min – max	20 – 44		19 – 33	***p=0.000000
Normal weight n(%)	30	13 (10.83)	17 (42.5)	
Pre-obese n(%)	65	47 (39.17)	18 (45)	
Moderate obesity n(%)	45	40 (33.33)	5 (12.5)	X^2=27.6
Severe obesity n(%)	16	16 (13.33)	0	***p=0.000015
Extreme obesity n(%)	4	4 (3.33)	0	
Waist circumference (cm)				
mean ±SD	96.1 ± 11.4		83.3 ± 9.9	t=6.35
min – max	74 – 129		65 – 104	***p=0.0000000

t(Student t-test) ***p<0.0001

Postmenopausal women had a significantly higher average BMI than perimenopausal women (31.2 ± 4.9 vs 28.8 ± 3.8; p=0.0033). There were 9 (15%) perimenopausal and 4 (6.7%) postmenopausal patients with normal weight. Postmenopausal patients were more often moderate and extremely obese (6.7% postmenopausal and none of perimenopausal women were moderate obese; 21.7% postmenopausal and 5% perimenopausal women were extremely obese).

The described differences in the distribution of patients with normal weight, overweight, moderate, severe and extreme obesity between the peri and postmenopausal subgroups were statistically significant (p=0.0079) [table 2].

Waist circumference had a significantly higher mean value in postmenopausal patients than in perimenopausal patients (98.9±12.4cm vs 93.7±9.7cm; p=0.018) [table 2].

Table 2. Distribution of peri and postmenopausal subgroup according to BMI and waist circumference

variable	**subgroups**			**p-level**
	n	**perimenopause**	**postmenopause**	
BMI (kg/m^2)				
mean ±SD	28.80 ± 3.8		31.22 ± 4.9	t=3.002
min – max	20 – 35		24 – 44	**p=0.0033
Normal weight n(%)	13	9 (15)	4 (6.67)	X^2=13.79
Preobese n(%)	47	24 (40)	23 (38.33)	**p=0.0079
Moderate obesity n(%)	40	24 (40)	16 (26.67)	
Severe obesity n(%)	4	0	4 (6.67)	
Extreme obesity n(%)	16	3 (5)	13 (21.67)	
Waist circumference (cm)				
mean ±SD	93.70 ± 9.7		98.58 ± 12.4	t=2.39
min – max	74 – 125		75 – 129	*p=0.018

t(Student t-test) *p<0.05 **p<0.01***p<0.0001

X^2 (Pearson Chi-square)

Patients with organic changes had a significantly higher BMI than patients with functional changes (p = 0.042). The mean BMI was 30.56 in the subgroup with organic changes and 28.72 in those with functional changes [table 3].

In the subgroup of patients with functional changes the majority were preobese - 22 patients (61.1%), while in the subgroup with organic changes the majority were moderate obese - 30 (35.7%). Severe obesity was registered only in the group with organic changes (in 4 patients) and 2 patients (5.6%) with functional and 14 (16.7%) with organic changes had extreme obesity. The described differences in the distribution of patients with normal weight, pre-obesity, moderate, severe and extreme obesity, between the subgroups with functional and organic changes, were statistically significant (p=0.016)[table 3].

Patients in the organic change subgroup had a significantly larger waist circumference than patients with functional endometrial changes (97.8cm vs 92.2 cm, p = 0.012) [table 3].

Table 3. Distribution of functional and organic changes subgroups according to BMI and waist circumference

variable	Type of HPA changes			p-level
	n	functional	organic	
BMI (kg/m^2)				
mean ±SD	28.72 ± 3.0		30.56 ± 4.98	t=2.05
min – max	21 - 35		20 – 44	*p=0.042
Normal weight n(%)	13	2 (5.56)	11 (13.1)	X^2=12.17
Pre-obese n(%)	47	22 (61.11)	25 (29.76)	*p=0.016
Moderate obesity n(%)	40	10 (27.78)	30 (35.71)	
Severe obesity n(%)	4	0	4 (4.76)	
Extreme obesity n(%)	16	2 (5.56)	14 (16.67)	
Waist circumference (cm)				
mean ±SD	92.2 ± 1.0		97.8 ± 11.6	t=2.54
min – max	75 – 129		74 – 127	*p=0.012

t(Student t-test); X^2(Chi-square) *p<0.05

Discussion

In our study, the most common pathological change of the endometrium is an endometrial polyp (in 45% of the respondents). In the study of Ozkan et al., it was determined that the connection between the appearance of endometrial polyps, metabolic syndrome and insulin resistance is possible. They found that body mass index (BMI), waist circumference, insulin levels, and the HOMA index of insulin resistance were significantly higher in the endometrial polyp group compared to the non-polyp control group. Metabolic syndrome was present in 71.7% of women in the study group and in 13.3% of those in the control group (p<0.001) [12].

Estrogens and progesterone regulate endometrial proliferation and differentiation, and endometrial polyps have both estrogen and progesterone receptors, which likely play a major role in their etiopathogenesis [13].

Obesity is one of the the most important risk factors for the occurrence of endometrial polyps. The metabolic syndrome was associated with an increased risk for endometrial cancer, and among the components of the syndrome, obesity/increased waist circumference was most associated with this cancer [14].

Kaya et al. investigated the association of benign pathological changes of the endometrium (polyp and atypical hyperplasia) with metabolic status (insulin resistance and metabolic syndrome). Obesity and waist circumference over 88cm were detected significantly more in the group with pathological changes compared to the control group (p=0.005 vs p<0.001) [15].

In our study, we made a comparison between subjects with functional and organic pathological changes of the endometrium. Patients with functional changes had a significantly lower body mass index than patients with organic changes (p=0.042). Also, patients from the group with functional changes had a significantly smaller waist circumference (92.2 ± 1.0 vs 97.8 ± 11.6cm, p=0.012).

In a meta-analysis by Renehan et al., where they investigated 19 studies with 17,804 subjects, they determined a significant positive association of an increase in BMI of 5 kg/m² with the occurrence of endometrial cancer (RR=1.59, p<0.0001) [16]. Aune et al. performed a meta-analysis of 32 prospective studies on the influence of anthropometric factors on the risk of endometrial cancer. In terms of body mass index, with its increase of 5 units, the relative risk was 1.54; with an increase in body weight by 5 kg, the relative risk was 1.16, while in relation to waist circumference, for a 10 cm increase, the relative risk was 1.27 [17].

In our study, we made a comparison between perimenopausal and postmenopausal women who underwent fractionated explorative curettage due to abnormal bleeding or ultrasound-diagnosed endometrial abnormality. Perimenopausal patients were younger and had a significantly lower BMI than postmenopausal patients (p=0.0033). Also, patients of the postmenopausal subgroup had a significantly larger waist circumference than those of the perimenopausal subgroup (mean value of 98.9±12.4cm vs 93.7±9.7cm; p=0.018).

Enzymes are present in adipose tissue that convert androgenic precursors produced in the ovaries and adrenal glands into estrogens [217]. After menopause, adipose tissue is a major site for estrogen synthesis through aromatization of adrenal estrogens. The general and abdominal adiposity present after menopause increases the level of insulin and IGF 1, which leads to a reduction in the synthesis of SHBG in the liver, its lower serum concentration, and thus a higher level of free estrogens. Higher concentrations of SHBG are associated with a reduced risk for endometrial cancer [18].

Conclusion

Patients with explorative curettage had a significantly higher body mass index and waist circumference than healthy women. Postmenopausal women had a significantly higher body mass index and waist circumference than perimenopausal women. Patients with organic endometrial changes had a significantly higher body mass index and waist circumference compared to those with functional changes.

Obesity is a clinical, but also a public health problem. As a public health problem, measures should be taken to modify lifestyle, diet and increase physical activity. The increasing incidence of endometrial carcinoma and its association with modifiable risk factors including obesity is critical to continue research for the prevention of this cancer.

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