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THE IMPACT OF OBESITY AND FAT DISTRIBUTION ON ENDOMETRIAL CANCER RISK IN POSTMENOPAUSAL PATIENTS

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Abstract

Endometrial cancer (EC**)** is the fourth most common cancer in women worldwide, with rising incidence partly due to changing reproductive trends and ever increasing obesity. Obesity, especially central adiposity, is linked with endometrial adenocarcinoma, possibly due to elevated estrogen and decreased sex hormone-binding globulin levels.

The study aims to evaluate the impact of obesity on endometrial malignancy and to determine whether central adiposity (measured by the waist-to-hip circumference ratio) serves as a better indicator of endometrial cancer risk than BMI.

In this cross-sectional study, we studied 164 postmenopausal patients from the University Clinic of Obstetrics and Gynaecology in Skopje. Patients were admitted to the hospital for histopathological examination of endometrial layer because of vaginal bleeding with endometrial thickness >4mm, or other sonographic endometrial abnormalities. Histopathological findings subdivided them into two categories: with malignancy (group I) or benign abnormality (group II). Standard examinations and measurements, including BMI and waist-to-hip ratio, were performed.

A significant association was observed between endometrial malignancy and obesity as measured by waist-to-hip ratio. In the distribution of data related to BMI and histopathological findings from the endometrial biopsy for Pearson Chi-square=8.35 and $p<0.01$($p=0.004$) there is a significant difference. For Odds Ratio=2.71 (95.%CI:1.36-5.38), patients who had a BMI ≥ 30 kg/m2 were 2.71 times more likely to have endometrial malignancy than patients who had a BMI <30 kg/m2, ($p<0.01$).

There is a significant difference in the shown distribution of data related to waist circumference/hip circumference and histopathological findings of endometrial sampling Pearson Chi-square=79.22 and $p<0.001$($p=0.000$). For Odds Ratio=40.89 (95.% CI:15.23-109.78), patients who had waist circumference/hip circumference ≥ 0.85 were 40.89 times more likely to have endometrial malignancy than patients who had waist circumference/hip circumference <0.85, ($p<0.001$). Upon analysing the contribution of central obesity determined by waist-to-hip ratio, it was found to have a more substantial impact (Wald = 37.76, $p < 0.001$) compared to BMI (Wald = 0.97, p= 0,32).

Our study confirms that obesity is a risk factor for endometrial malignancy. Furthermore, fat distribution proves to be a more crucial and accurate indicator of endometrial cancer risk than overall obesity. The statistical significance of the waist circumference to hip circumference ratio exceeded that of BMI.

Therefore, even if a patient has a normal BMI, but a waist-to-hip circumference ratio greater than 0,80, she should be considered at increased risk for endometrial malignancy and should be closely monitored in the future in order to detect any malignant changes.

Keywords*:* endometrial cancer, body mass index, waist circumference - hip circumference ratio, obesity.

Introduction

Endometrial cancer (EC) is the fourth most frequently diagnosed cancer among women worldwide [1]. Globally, endometrial cancer has been increasing in incidence over the years mainly due to the changes in reproductive patterns such as postponing childbirth and increase in obesity rates [2].

The incidence of EC is higher in high-income countries, however it has been increasing in low- and middle-income countries as well. [3]. In the Republic of North Macedonia, endometrial cancer stands as the second most prevalent malignant neoplasm in women, second only to breast cancer.

In 2020, there were 360 diagnosed cases, with 80 fatalities, equating to an age-standardized incidence rate of 22.3 per 100,000 women [4].

Major risk factors for EC encompass comorbidities such as diabetes mellitus and hypertension, and conditions linked to prolonged exposure to estrogens [3].

Such conditions include hormone replacement therapy (HRT), chronic anovulation, early menarche and/or late menopause, nulliparity, and obesity.[5].

Obesity is known as a risk factor for many cancers, including endometrial adenocarcinoma [6,7]. Excess body weight is a known independent risk factor for EC, and obese patients show a 4.7-fold increased risk compared to the general population to develop the neoplasm [8].

Obesity may increase the risk of endometrial cancer by several potential mechanisms. Weight gain is largely reflected in body fat accumulation. Excessive conversion of androstenedione to oestrone, and decreased serum levels of the sex hormone-binding globulin (SHBG), related to obesity, create an estrogen-rich environment that stimulates the development of endometrial cancer cells [9]. More specifically, obese women are exposed to prolonged unopposed estrogens during early adulthood, which results in an increased risk of endometrial cancer [10].

In postmenopausal women, the mechanism of endometrial cancer development can be explained by the peripheral conversion of androgens into estrogens caused by an increase in peripheral fat stored. This hormonal alteration stimulates the proliferation of endometrial cells by inhibiting apoptosis, thus promoting angiogenesis [11].

An association between obesity and EC has been shown in a variety of epidemiologic studies [12]. The evidence for the adverse effects of overall adiposity is quite convincing. Excess adiposity, often defined by body mass index (BMI) ≥ 30, is an established risk factor for endometrial cancer [13,14].

However, BMI reflects both fat and fat-free mass, which may have different associations with disease risk, and it also does not assess fat distribution, which varies considerably even among individuals with a similar BMI [15].

The association of body fat distribution with endometrial cancer has been less well characterized. Body mass distribution refers to the way fat is distributed around different parts of the body. While some studies have shown a positive association with upper-body or central obesity, others have found no association with waist/hip ratio or have found an association that disappeared after an adjustment for BMI [12].

The distribution of body fat, in particular central adiposity, is linked to several metabolic abnormalities that are associated with endometrial cancer development [16].

Although several studies have evaluated central adiposity, typically assessed by waist circumference, waist-to-hip ratio or waist-to-height ratio, in relation to the risk of endometrial cancer, it remains unclear whether central adiposity contributes to risk irrespective of overall adiposity [17].

Objectives: The study aims to evaluate the impact of obesity on endometrial malignancy and to determine if central adiposity (measured by the waist-to-hip circumference ratio) serves as a better indicator of endometrial cancer risk than BMI.

Material and Methods

The study was conducted at the University Clinic of Obstetrics and Gynaecology in Skopje, North Macedonia, between December 1, 2015, and July 31, 2017. Given the varied biological mechanisms by which adiposity influences endometrial cancer risk in premenopausal versus postmenopausal women, our cross-sectional study focused on 164 postmenopausal patients. These patients, admitted to the Gynaecology Department for endometrial sampling, were defined as postmenopausal based on an absence of menstrual periods for at least 12 months prior.

The inclusion criterion was postmenopausal patients with an endometrial thickness exceeding 4mm and/or vaginal bleeding. Patients experiencing postmenopausal bleeding due to hormone replacement therapy or vaginal bleeding resulting from vaginal atrophy or other systemic diseases were excluded. Histopathological analysis further subdivided these groups into two groups: Group I: Patients with endometrial malignancies, and group II: Patients with benign endometrial lesions. Prior to admission, all patients underwent a vaginal examination and transvaginal ultrasonography. They emptied their bladders and were examined in the lithotomy position by a gynaecologist. If a thickened endometrium was detected, with or without vaginal bleeding, the patient was recommended for further endometrial evaluation.

Upon obtaining written consent, a structured in-person interview was conducted to gather data on demographic factors, menstrual and reproductive history, and height and weight history throughout their life. Measurements for current weight, standing height, and waist and hip circumference were also taken. Girth measurements were done using cloth tape, and body weight was determined with electronic scales.

Adiposity estimations utilized body weight and BMI, with body fat distribution gauged through the waist-to-hip circumference ratio. Body mass index (BMI) is a measure of body fat based on height and weight. The formula for BMI is weight in kilograms divided by height in meter squared. People with BMI ≥ 30 kg/m2 are obese. The waist–hip ratio is the dimensionless ratio of the circumference of the waist to that of the hips. This is calculated as waist measurement divided by hip measurement (W⁄H). Patients who had waist circumference/hip circumference ≥0.85 were considered ac upper adipose women.

Patients exhibiting thickened endometrium underwent endometrial sampling procedures such as dilatation and curettage or hysteroscopy. These procedures were consistently performed by the same gynaecologist under short-term intravenous anaesthesia in the operating room. Subsequent endometrial biopsies were analyzed by a pathologist at the Institute of Pathology at the Faculty of Medicine. Based on these analyses, patients were further divided into the previously mentioned groups I and II.

Statistical Analysis

All data were entered into a dedicated form, creating a database for statistical analysis. Analysis was executed utilizing STATISTICA 7.1 and SPSS 17.0 for Windows. Univariate regression determined potential relationships between endometrial malignancy and clinical variables (BMI and waist/hip circumference ratio). A p-value under 0.05 was deemed statistically significant.

Results

The mean age of the patients was 60, 05±9, 09; ±95%CI: 58, 80-61, 30. The youngest patient was 40 years and the oldest was 85 years old.

Histopathological analysis at the exanimated groups (I and II) showed positive findings at 47 patients (28, 66%) with endometrial cancer and atypical endometrial hyperplasia at 7 (4, 27%). Graph No. 1 illustrates that an additional 110 patients exhibited benign pathology. .

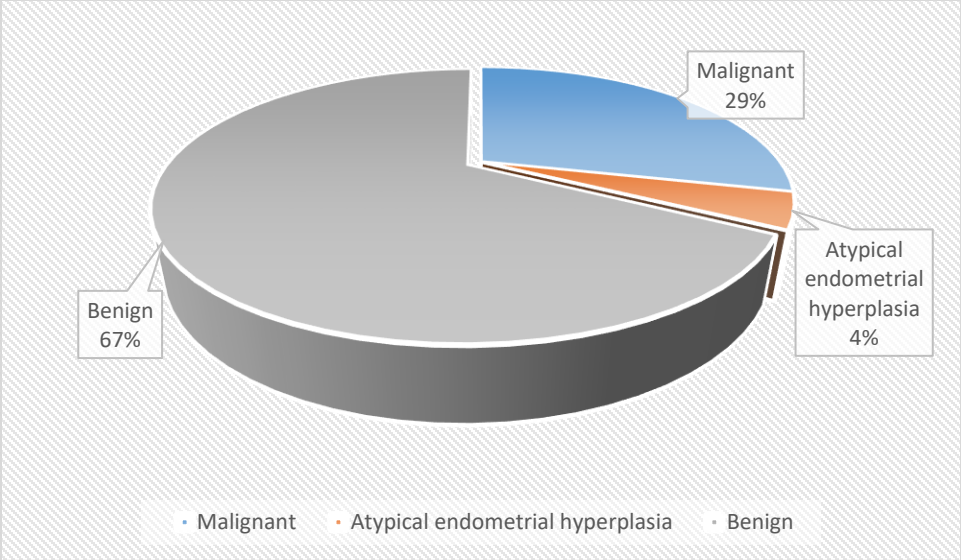

Figure 1. Histopathological findings at examined groups I+II

Table 1 and Figure 2 show data related to BMI in patients and histopathological findings of endometrial sampling.

In 78 patients who had BMI <30 kg/m2, malignant findings were registered in 17 (21.79%) patients and benign findings were registered in 61 (78.21%) patients.

In 86 patients who had a BMI ≥ 30 kg/m2, malignant findings were registered in 37 (43.02%) patients, and benign findings were registered in 49 (56.98%) patients.

In the distribution of data related to BMI and histopathological findings from the endometrial biopsy for Pearson Chi-square=8.35 and p<0.01(p=0.004) there is a significant difference.

For Odds Ratio=2.71 (95.%CI:1.36-5.38), patients who had a BMI ≥ 30 kg/m2 were 2.71 times more likely to have endometrial malignancy than patients who had a BMI <30 kg/m2, the indication is significant for p<0.01.

Table 1. BMI and histopathological analysis

	BMI	Histopathological analysis		All
		Malignant and atypical hyperplasia	Benign	
No	<30 кг/м^2	17	61	78
%		21,79%	78,21%	
No	≥ 30 кг/м^2	37	49	86
%		43,02%	56,98%	
No	All Grps	54	110	164

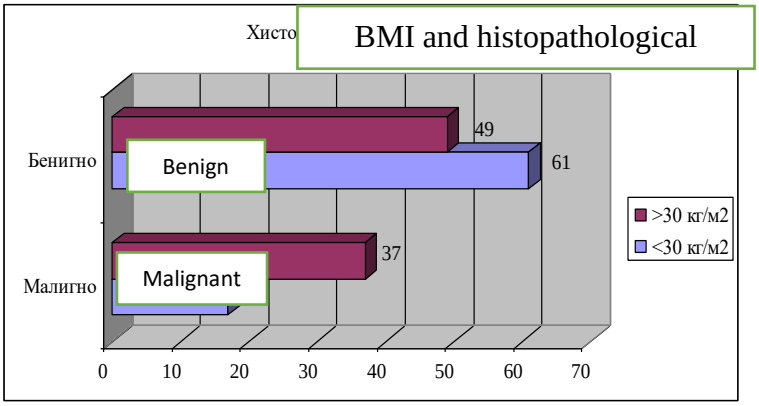

Figure 2. BMI and histopathological analysis

Table 2 and graph 3 show data related to waist circumference/hip circumference in female patients and histopathological findings of endometrial sampling.

In 98 patients who had waist circumference/hip circumference <0.85, malignant findings were registered in 6 (6.12%) patients, and benign findings were registered in 92 (93.88%) patients. In 66 patients who had waist circumference/hip circumference ≥ 0.85, malignant findings were registered in 48 (72.73%) patients and benign findings were registered in 18 (27.27%) patients.

There is a significant difference in the shown distribution of data related to waist circumference/hip circumference and histopathological findings of endometrial sampling Pearson Chi-square=79.22 and p<0.001(p=0.000).

For Odds Ratio=40.89 (95.%CI:15.23-109.78), patients who had waist circumference/hip circumference ≥ 0.85 were 40.89 times more likely to have endometrial malignancy than patients who had waist circumference/hip circumference <0.85, the indication is significant at p<0.001.

Table 2. Waist circumference/hip circumference & histopathological analysis

	waist circumference/ hip circumference	histopathological analysis		All
		Malignant	Bengn	
No	<0,85	6	92	98
%		6,12%	93,88%	
No	≥ 0,85	48	18	66
%		72,73%	27,27%	
No	All Grps	54	110	164

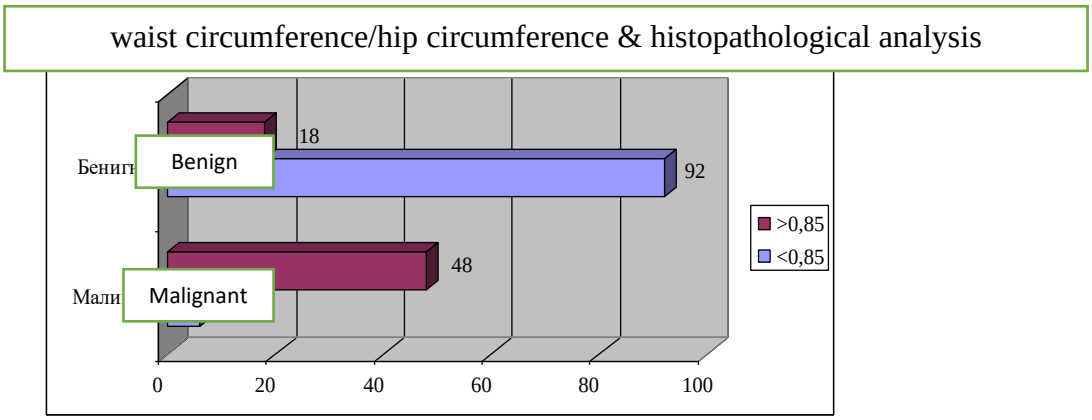

Figure 3. Waist circumference/hip circumference & histopathological analysis

The results regarding the impact of BMI and waist circumference/hip circumference, for endometrial malignancy are shown in Table 3.

When determining the significance of the contribution of both components, it was determined that waist circumference/hip circumference had bigger impact (Wald=37.76 / p<0.001 (p=0.000), than the BMI (Wald=0.97 / p>0.05 (p=0.32).

Table 3. Endometrial malignancy and BMI / waist circumference/hip circumference

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
BMI(1)	-,60	,61	0,97	1	,32	,55	,17	1,81
waist circumference/hip circumference (1)	4,36	,71	37,76	1	,000	78,60	19,54	316,18

a. Variable(s) entered on step 1: BMI, waist circumference/hip circumference

Discussion

Obesity is one of the most common disorders observed in medical practice and is a major public health problem. Being overweight is becoming an increasingly common phenomenon that occurs in developed countries and in developing countries, because of the new lifestyle of the population. According to the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund (WCRF), approximately 20% of all cancer cases can be associated with obesity, especially endometrial, oesophagus (adenocarcinoma), colorectal, prostate, renal and postmenopausal breast cancers [18].

Recent data in the literature emphasize that overweight in women is becoming a disease of modern society, and is one of the reasons for the increased incidence of endometrial malignancy [19].

It has been concluded that with increasing body weight, the risk of EC increases significantly. Prospective studies have revealed a 1.59 (95% CI 1.50–1.68) increased risk of EC for each gain of 5 kg/m2 [3].

In patients with an overweight of 9.5-22.6 kg, the risk of EC is increased 3-fold, and even 10-fold in those with an overweight of more than 22.6 kg (20).

The effect of obesity on endometrial cancer risk has been a topic of interest for decades. Since Mack et al. reported a positive association between adiposity and the risk of endometrial cancer in the early 1970s, a number of investigators have explored the role of obesity in the development of endometrial cancer, primarily using measurements of body weight and indices of relative weight as an indicator of overall adiposity [21].

Overweight patients are unfortunately increasingly recorded in our clinical practice too, which was one of the reasons why we have decided to investigate the predictive value of BMI and waist circumference/hip circumference. The results from our study proved that endometrial cancer risk was positively associated with both measures of adiposity (BMI, and waist-to-hip ratio). When determining the significance of the contribution of both components, it was deduced that waist circumference/hip circumference had the bigger impact.

BMI is the most commonly used measure of adiposity in studies relating adiposity to the risk of endometrial cancer. After the proven significance of BMI by univariate analysis, Burbos included this parameter in his scoring systems DEFAB and DFAB [21,22].

On the other hand, in the research of Giannella and Opolskiene, the results of the univariate analysis showed that BMI had no significant influence in determining the risk for the presence of EM [24,25]. In our population, the univariate analysis for the patients with a BMI $\geq$ 30kg/m2 showed that they have 2.71 times higher probability of endometrial malignancy than patients with BMI < 30kg/m2.

The role of fat deposition and distribution in the development of endometrial cancer has received much attention recently. It has been related to an increased level of estrogen and a reduced level of sex hormone-binding globulin in patients with central and upper body obesity. Previous prospective studies examining the independent effect of central adiposity on endometrial cancer risk have reported conflicting results [12, 14, 19, 26-32].

Many authors like Petridou, Xu, Kitson, and Aune specifically highlight the importance of the type of obesity in their studies, reporting that the distribution of adipose tissue in the upper body is a more significant risk factor than the increased BMI [12, 19, 26, 27].

While several studies have found that body fat distribution confers additional risk for endometrial cancer [12], one study found that the positive association between waist-to-hip ratio and the disease disappeared after adjusting for BMI [28]. Meanwhile, a Japanese study observed an increased risk associated with fat distribution, but not with overall adiposity [29].

A special emphasis on overweight is placed in the predictive model for endometrial cancer formulated by Kitson et al., as part of the program for the prevention of this malignancy [19].

In addition to BMI, they include the ratio of waist circumference/hip circumference in their model. The authors point out that if this ratio is greater than 0.80, the patients are classified as being in a risk group, even if they have a normal BMI. By utilizing this predictive factor, they detect high-risk women, and with a special strategy for their evaluation, the malignant change can be detected in time. Therefore, they highlight the ratio of waist circumference/hip as a more significant factor in predicting endometrial cancer. The same results were confirmed in the meta-analysis in Aune's review paper and in the California Teachers' Study. [27,30].

On the other hand, the Nurses'Health Study did not report an independent association with these measures, [31] while the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort reported an independent association with waist circumference, but not waist-to-hip ratio [32].

In one of the most recent analyses, a small increase in risk remained for waist circumference and waist-to-hip ratio after adjusting for BMI, suggesting that central adiposity as reflected by these measures may confer risk above and beyond overall adiposity [14].

In our population, the univariate analysis for the patients with waist circumference/hip circumference $\geq$ 0.85 were 40.89 times more likely to have endometrial malignancy than patients with waist circumference/hip circumference <0.85.

Conclusion

The results of our study have proved that obesity is a risk factor for endometrial malignancy and fat distribution is a more significant indicator of endometrial cancer risk than overall obesity. The statistical significance of the waist circumference to hip circumference ratio exceeds that of BMI. Therefore, even if a patient has a normal BMI, but a waist-to-hip circumference ratio greater than 0,80, she should be considered as being at an increased risk of endometrial malignancy. Such patients should be closely monitored in future in order to detect any malignant changes.

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