

## Utility of the Ultrasound Evaluation of Intraoperative Fat in Correlation with Endometrial Cancer

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Received: 28 November 2010 / Accepted: 21 February / Published online: 7 March 2011

### Abstract

*Introduction:* In the context of endometrial cancer, visceral obesity as a risk factor is associated with a chronic inflammatory process, confirmed by the increase in inflammatory marker levels. *Material and Method:* The study is a case-control analysis including 2 groups of patients: group I – 50 patients diagnosed with endometrial cancer, group II – 70 patients without gynecological pathology or inflammatory disorders (control group). The diagnosis of endometrial cancer was made following histopathological examination that evaluated the tissue material obtained following endometrial biopsy. After clinical examination and anthropometric measurements, these patients underwent ultrasound and computer tomography examination by which intraoperative fat was determined. All parameters were included in the study database. *Results:* A significant correlation coefficient was also found between visceral fat evaluated by CT and visceral fat assessed by US ( $r = 0.96$ ,  $p < 0.0001$ ). In the case of the control group, the mean visceral fat area was  $159.14 \pm 42.5$  cm<sup>2</sup>, while in the group of patients with endometrial cancer, the mean visceral fat area was  $251.37 \pm 59.78$  cm<sup>2</sup>. Thus, there is a statistically significant difference in intraoperative fat between the two groups ( $p < 0.0001$ ). *Conclusions:* A visceral fat area larger than 250 cm<sup>2</sup> is a risk factor for endometrial cancer. The measurement of visceral fat by US can be a screening method for endometrial cancer in obese patients.

**Keywords:** Endometrial cancer; Visceral obesity; Ultrasound.

### Introduction

Obesity is an endemic disorder of the 21<sup>st</sup> century, with a continuously increasing prevalence, particularly in young persons. Many studies have demonstrated that obesity is closely correlated

with the levels of visceral fat deposits [1]. A visceral fat area larger than 100 cm<sup>2</sup> at umbilical level is a risk factor for cardiac disorders, diabetes mellitus, and is accepted as visceral obesity [2].

Obesity, predominantly intra-abdominal visceral adipose tissue, is associated with insulin resistance, hyperinsulinemia, and increased serum fatty acid concentrations. In developed countries, endometrial cancer is associated with obesity in a proportion of 40% [3]. In the context of endometrial cancer, visceral obesity as a risk factor is associated with a chronic inflammatory process, confirmed by an increase in the inflammatory markers, C reactive protein, interleukin 6, tumor necrosis factor  $\alpha$  (CRP, IL6, TNF $\alpha$ ) in the systemic circulation of obese patients. This chronic proinflammatory state is in turn a risk factor for endometrial cancer.

Starting from the idea that in modern society the prevalence of obesity is increasing and that adipose tissue is directly correlated with a number of disorders, that a series of paraclinical investigations specific for adipose tissue are available, *adipose tissue dysfunction* is currently considered as an individual pathological condition. Adipose tissue is no longer considered to be just an energy storage organ, but a real endocrine organ. Investigations such as computed tomography (CT) and nuclear magnetic resonance (NMR) are excellent methods for the assessment of visceral fat. Although these imaging techniques have a good sensitivity and specificity, they have the disadvantage of being expensive, as well as of exposing the patient to ionizing radiation in the case of CT.

The development of ultrasound (US) has made possible the exact measurement of parameters, based on which visceral fat can be quantified [4,5]. In order to increase the accuracy of the assessment, the correlation of the various distances measured has been attempted, which has resulted in a number of indices such as the subcutaneous fat index, the visceral fat index.

The study aims to assess the presence of a correlation between the measurement of abdominal fat by ultrasound and computed tomography and tests the use of abdominal ultrasound for the evaluation of visceral fat, as an alternative for the identification of patients at risk for developing endometrial cancer.

## Material and Method

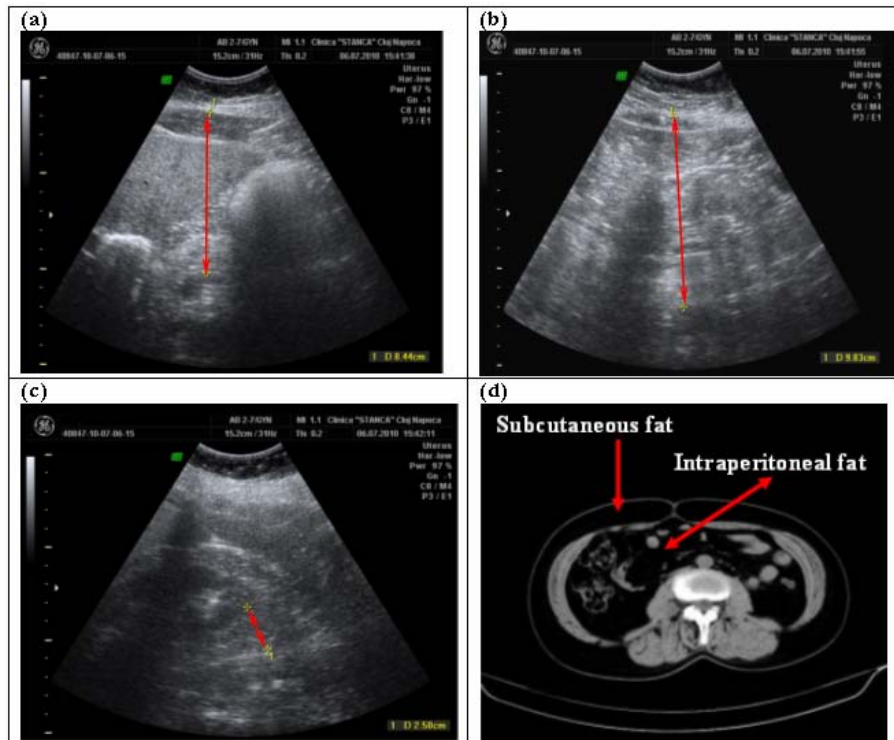
The study is a case-control analysis including 2 groups of patients: group I – 50 patients diagnosed with endometrial cancer, group II – 70 patients without gynecological pathology or inflammatory disorders (control group). The diagnosis of endometrial cancer was made following histopathological examination that evaluated the tissue material obtained following endometrial biopsy. Endometrial biopsy was performed in the case of important metrorrhagia, in the case of metrorrhagia in climax, as well as in the case of the ultrasound detection of increased endometrial thickness.

After clinical examination and anthropometric measurements (BMI, Ac), these patients underwent ultrasound examination by which intraperitoneal fat was determined.

BMI was calculated using the formula  $BMI = \text{weight (kg)} / [\text{height (m)}]^2$ . AC (cm) was measured in orthostatism, at umbilical level. Ultrasound exploration (Voluson 730) was performed in dorsal decubitus at the end of a normal expiration, after a digestive rest period of 12 hours, in order to assess visceral fat deposits. The visceral fat area determined by ultrasound was calculated using the formula  $9.008 + 1.191 \times [\text{distance between the inner side of the right abdominal muscle and the splenic vein (mm)}] + 0.987 \times [\text{distance between the inner side of the right abdominal muscle and the posterior wall of the aorta (mm)}] + 3.644 \times [\text{fat thickness in the posterior wall of the right kidney (mm)}]$  [6] (Figure 1).

In order to check the validity of the formula in 10 patients who underwent ultrasound examination, CT was also performed in dorsal decubitus at the end of a normal expiration, after a digestive rest period of 12 hours, and the results obtained by the two imagistic examinations were subsequently compared.

The informed consent of all patients was obtained. All parameters were included in the study database, using the statistical analysis software SPSS version 13.0 and Microsoft Excel with the Analysis Tool Pack.



**Figure 1.** (a) Distance between the inner side of the right abdominal muscle and the splenic vein. (b) Distance between the inner side of the right abdominal muscle and the aorta. (c) Measurement of perirenal fat. (d) Intra-peritoneal fat evaluated by CT

#### Statistical Analysis

In the case of the comparison of two means for independent samples, the Student t test or the Mann-Whitney test for rank comparison were used. The normal distribution was tested with Kolmogorov-Smirnov test. The correlation analysis were made by using Pearson correlation coefficient or Spearman correlation coefficient. In order to find the cutt-off of a quantitative variable we used receiver operating characteristic (ROC) curved analysis. For multivariate analysis , logistic regression was used

Statistical calculations were performed using the applications SPSS 13.0 and Microsoft EXCEL. The significance threshold was  $\alpha = 0.05$ .

#### Results

The patients' data are described in Table 1.

There was a significant difference in weight between the two groups ( $p < 0.001$ ), the mean weight of the control group being smaller than the mean weight of the group with endometrial cancer (Table 1). There was a significant difference of intra-peritoneal fat between the two groups ( $p < 0.001$ ), the mean intra-peritoneal fat between of the control group being smaller than the mean intra-peritoneal fat of the group with endometrial cancer (Table 1). There is a significant difference in BMI and AC between the control group and the group with endometrial cancer ( $p < 0.0001$ ).

In cases group intra-peritoneal fat US formula was corelated with weight (Spearman  $r = 0.84$ ,  $p < 0.0001$ ), IMC ( $r = 0.76$ ,  $p < 0.0001$ ) and AC ( $r = 0.72$ ,  $p < 0.0001$ ). Intra-peritoneal fat US formula in cases group was not corelated with age ( $r = 0.17$ ,  $p = 0.23$ ), menarche ( $r = -0.11$ ,  $p = 0.45$ ), menopause ( $r = 0.15$ ,  $p = 0.39$ ) and number of children ( $r = 0.09$ ,  $p = 0.57$ ). In the same group age was not correlated with weight ( $r = 0.12$ ,  $p = 0.42$ ), IMC ( $r = 0.17$ ,  $p = 0.24$ ) and AC ( $r = 0.18$ ,  $p = 0.23$ ).

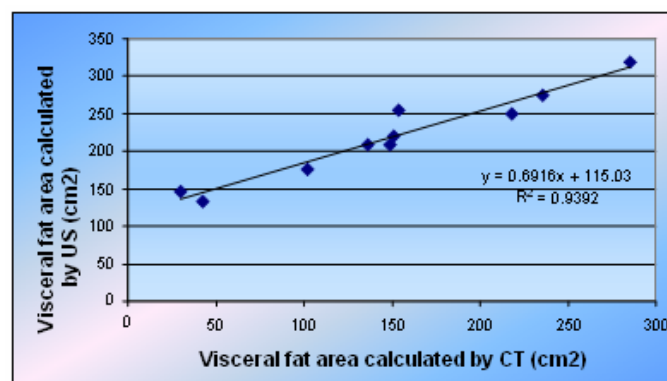
**Table 1.** Characteristics of the patients included in the study

		N	m	StDev	StdErr	95% CI for m		Min	Max	p
AGE	Control	70	55.47	9.07	1.08	53.31	57.63	42.00	80.00	0.004
	Case	49	60.57	9.92	1.42	57.72	63.42	41.00	80.00	
WEIGHT (kg)	Control	70	63.71	11.72	1.40	60.92	66.51	40.00	100.00	<0.0001
	Case	49	85.33	13.67	1.95	81.40	89.25	62.00	112.00	
BMI	Control	70	24.55	4.00	0.48	23.60	25.51	16.90	36.40	<0.0001
	Case	49	32.49	4.66	0.67	31.15	33.82	22.80	42.70	
AC	Control	70	76.37	8.58	1.03	74.33	78.42	64.00	119.00	<0.0001
	Case	49	97.57	11.78	1.68	94.19	100.96	71.00	123.00	
Intraperit fat US formula (mm)	Control	70	159.14	42.50	5.08	149.01	169.27	93.15	297.62	<0.0001
	Case	49	251.37	59.78	8.54	234.20	268.54	141.56	361.83	
Menarche	Control	70	12.01	0.88	0.10	11.81	12.22	11.00	14.00	0.63
	Case	47	12.15	1.96	0.29	11.57	12.72	9.00	16.00	
Menopause	Control	54	51.28	2.69	0.37	50.54	52.01	45.00	55.00	0.50
	Case	35	49.06	10.69	1.81	45.39	52.73	3.00	56.00	
No of children	Control	70	1.71	0.78	0.09	1.53	1.90	0.00	3.00	0.83
	Case	47	1.70	1.12	0.16	1.37	2.03	0.00	5.00	

N = sample size; m = arithmetic mean; StDev = standard deviation; StdErr = standard error; 95% CI for m = 95% confidence interval for mean; Min = minimum value; Max = maximum value

In control group intraperitoneal fat US formula was correlated with weight ( $r=0.79$ ,  $p<0.0001$ ), IMC ( $r=0.60$ ,  $p<0.0001$ ) and AC ( $r=0.56$ ,  $p<0.0001$ ). Intraperitoneal fat US formula in control group was not correlated with age ( $r=-0.23$ ,  $p=0.06$ ), menarche ( $r=-0.05$ ,  $p=0.68$ ), menopause ( $r=-0.05$ ,  $p=0.73$ ) and number of children ( $r=0.21$ ,  $p=0.09$ ). In the same group age was not correlated with weight ( $r=-0.19$ ,  $p=0.13$ ), IMC ( $r=0.06$ ,  $p=0.63$ ) and AC ( $r=0.03$ ,  $p=0.79$ ).

For the 10 patients in who underwent ultrasound examination and CT, the Pearson correlation coefficient between the body weight and visceral fat assessed by CT ( $r =1$ ,  $p<0.0001$ ) and US ( $r=0.98$ ,  $p<0.0001$ ) was statistically significant. A significant Pearson correlation coefficient was also found between visceral fat evaluated by CT and visceral fat assessed by US ( $r=0.96$ ,  $p<0.0001$ ) (Figure 2).



**Figure 2.** Correlation between the visceral fat area assessed by US and CT

According to the ROC curve, for the group with endometrial cancer, the cutoff value of BMI is 25.6 ( $p<0.0001$ ) and of AC is 84.5 ( $p<0.0001$ ) (Figures 3 and 4).

The cutoff value of intraperitoneal fat for the group with endometrial cancer is 250 cm<sup>2</sup> ( $p<0.0001$ ) (Figure 5).

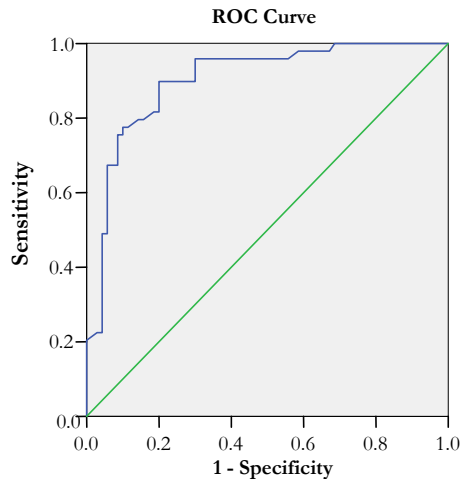


Figure 3. ROC curve for BMI

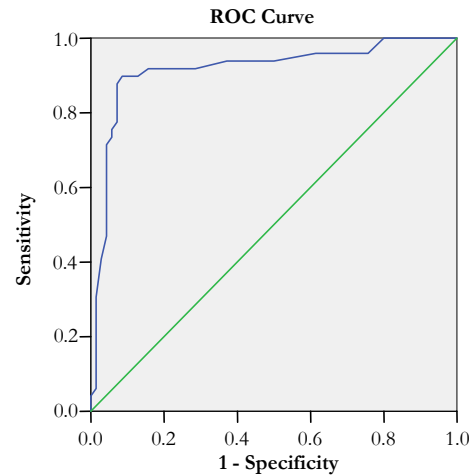


Figure 4. ROC curve for AC

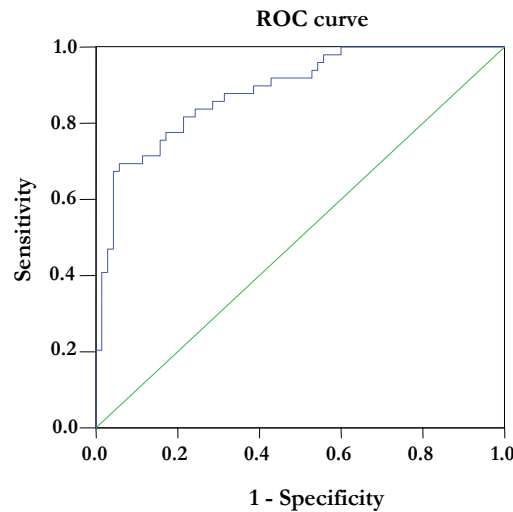


Figure 5. ROC curve for AC

## Discussion

Depending on the predominance of adipose tissue and on its location, obesity can be android or gynoid. The best indicator in the determination of the type of obesity is the waist/hip ratio. Waist is assessed by the measurement of the smallest circumference located between the costal margin and the iliac crest, while hips are assessed by measuring the largest circumference from the iliac crest to the thighs.

Android obesity is characterized by the predominance of adipose tissue in the central area of the body, at abdominal wall and visceral-mesenteric level. Gynoid obesity is characterized by the predominance of adipose tissue in the lower body area, in the buttock and thigh region. Women with android obesity have an increased adrenal gland activity, with the secondary increase in ACTH and cortisol secretion. Android obesity is associated with hyperinsulinemia, decreased glucose tolerance, diabetes mellitus, increased secretion of androgens and testosterone, as well as a decrease in sex hormone binding globulin (SHBG) [7].

The association of android obesity with hyperinsulinemia can be explained by three mechanisms [8]: ■ Android obesity is more catecholamine-sensitive and less insulin-sensitive, which causes an increase in free fatty acid concentrations and leads to

hyperglycemia; ▪ Androgens inhibit the action of insulin at hepatic and peripheral level; and ▪ The hepatic extraction of insulin is inhibited by androgens and free fatty acids.

Studies have demonstrated that insulin and insulin growth factor 1 (IGF1) inhibit SHBG secretion in hepatocytes, thus explaining the reverse proportionality between body weight and SHBG levels [9].

Anthropometric parameters (BMI, AC, the bicipital and tricipital skin fold, the waist/hip ratio) can be a rapid, easy to perform, non-invasive method for the evaluation of regional adiposity, particularly in epidemiological studies [2]. Obesity is closely correlated with visceral fat deposit levels [10]. Some studies have tried to establish the relationship between AC threshold values in order to define visceral obesity, which is in turn a risk factor for a series of pathological conditions [11]. In 2001, WHO reported as AC threshold values for metabolic syndrome among the USA population 102 cm for men and 88 cm for women, while in the case of Japanese, values are 85 for men and 90 for women [12]. In this study, the group of patients with endometrial cancer had an AC cutoff value of 84.5, which shows a direct proportional relationship between abdominal obesity and endometrial cancer.

The most widely used index for the assessment of weight is BMI. Depending on this index, the following are differentiated [13]: ▪ normal weight → BMI between 18.5 and 25; ▪ overweight → BMI between 25 and 30; and ▪ obesity → BMI  $\geq$  30.

In our study, the limit of BMI for which this represents a risk factor for endometrial cancer is 25.6, which demonstrates that not only obese women are at increased risk for developing endometrial cancer, but also overweight women.

There are studies supporting the fact that among patients considered to have visceral obesity assessed based on BMI (higher than 25), only 66% have a visceral fat area larger than 100 cm<sup>2</sup> [14]. On the other hand, the prevalence of complications was increased in patients with a visceral fat area larger than 100 cm<sup>2</sup>, even if these were not obese [15]. These results suggest that weight and BMI are not useful for the quantification of visceral fat.

For a much more accurate quantification of the amount of body fat and for a much more rigorous evaluation of the distribution of adipose tissue, the use of various imaging methods was initiated. CT and NMR were considered to be the most reliable imaging methods for the assessment of adipose tissue, as well as of its distribution. Because of the high costs and the limited use of CT and NMR, ultrasound started to be increasingly used for the evaluation of subcutaneous adipose tissue, of visceral adipose tissue. This study supports the idea that ultrasound can be an alternative method for the assessment of intra-abdominal fat, based on the close correlation between the values of visceral fat evaluated by CT and US, which is also supported by previous studies [16,17].

Armellini et al. [16] use the distance from the inner side of the right abdominal muscle to the posterior wall of the aorta as an indicator of the visceral fat volume. The difficulty of this technique consists of the fact that the aorta is not always detectable, particularly in obese persons, which is why some studies measure the distance from the inner side of the right abdominal muscle to the anterior vertebral wall, which is easier to identify [16]. Depending on the values obtained following measurements, patients can be divided into visceral and non-visceral obese patients. In this study, for a more accurate assessment of visceral fat, we used the measurement of three distances as follows: the distance between the inner side of the right abdominal muscle and the splenic vein, the distance between the inner side of the right abdominal muscle and the posterior wall of the aorta, the fat thickness in the posterior wall of the right kidney. The measuring of three distances allows for an increased accuracy of the assessment of visceral fat, all the more so as all these distances are located in the abdomen, without including buttock or thigh fat. Thus, android obesity is mainly evaluated.

The adipocyte is the central element that integrates multiple metabolic and endocrine signals. This cell is the source of many bioactive peptides that play an essential role in the modeling of insulin resistance and inflammation: TNF $\alpha$  (tumor necrosis factor), resistin, adiponectin, leptin, adiponectin, angiotensin, prostaglandins, IL6 (interleukin), tissue factor, steroids, TGF $\beta$  (transforming growth factor), MMPs (matrix metalloproteinases), IGF1, and PAI1 (plasminogen

activator inhibitor) [18].

The production of proinflammatory cytokines (TNF $\alpha$ , IL6, CRP) plays an important role in the genesis of endometrial cancer, but its mechanisms are not completely understood. In the context of endometrial cancer, visceral obesity as a risk factor is associated with a chronic inflammatory process, confirmed by the increased levels of inflammatory markers: TNF $\alpha$ , IL6, CRP in the systemic circulation of obese patients [19].

A possible explanation of the production of acute phase cytokines and proteins by the adipocyte may be the response to hypoxia occurring in the fat deposit area, which develops with the progression of obesity. Vascularization, which is less important in white adipose tissue compared to brown adipose tissue, is insufficient to maintain normal O<sub>2</sub> levels. By the agglutination of adipocytes, hypoxia intensifies, and the resulting inflammatory response increases blood flow and stimulates angiogenesis [20].

The theory according to which obesity through inflammation is a risk factor for endometrial cancer is supported by various hypotheses [13, 21]: ■ Estrogens unopposed by progesterone have an inflammatory effect on the endometrium; ■ Chronic endometrial inflammation is a risk factor for endometrial cancer; ■ NSAIDs inhibit endometrial cancer cells in vitro; and ■ The suppression of menstruation in laboratory animals by the long-term administration of NSAIDs.

In this study, anthropometric indices (AC, BMI) are significantly higher in the group with endometrial cancer compared to the control group, which suggests that body weight and obesity are risk factors for endometrial cancer, in accordance with the literature data [22, 23]. Also, the visceral fat area is larger in the case of patients with endometrial cancer, which supports the idea of visceral obesity as a risk factor for endometrial cancer.

The correlation coefficient between the visceral fat area assessed by US and the visceral fat area assessed by CT is 0.98, suggesting that the evaluation of visceral fat by US is as rigorous as by CT, which is in accordance with other literature studies [16].

Given that there is no effective screening method available for endometrial cancer and that US allows for a reliable assessment of visceral fat, which is a risk factor for endometrial cancer, it may be concluded that in obese persons, the measurement of visceral fat can be a predictive factor for endometrial cancer.

## **Conclusions**

1. There are no significant differences between the visceral fat area measured by CT compared to US.
2. A visceral fat area larger than 250 cm<sup>2</sup> is a risk factor for endometrial cancer.
3. The measurement of visceral fat by US can be a screening method for endometrial cancer in obese patients.

## **Ethical Issues**

The informed consent of all patients was obtained. The Ethics Commission from the "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca approved the study.

## **Conflict of Interest**

The authors declare that they have no conflict of interest

## **Acknowledgements**

Technical support was offered by Psihomed, who performed the CT examination.

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