The corelation between the endometrial thickness and insulin resistance in postmenopausal obese women

A pilot study

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Abstract

Background and Aims: *To estimate the significance of insulin, estrogens and central obesity on the endometrial thickness measured by ultrasound in postmenopausal obese women.* ***Materials and Methods:*** *14 postmenopausal insulin-resistant obese women and 11 postmenopausal noninsulin-resistant obese women were involved in this study. The anthropometric measurements included waist circumference (WC) and body mass index (BMI). Estimates of insulin resistance were derived from the HOMA index (basal glucose mmol/l x basal insulin μIU/ml/22.5); insulin-resistant women were defined by HOMA >3. Blood samples were drawn the morning after an overnight fast. Real-time ultrasonography was done with a 5 MHz vaginal transducer.* ***Results:*** *Endometrial thickness measurements ranged from 5 to 20 mm (median value 6.00 mm) in insulin-resistant obese women and 4 to 8 mm (median value 4.00 mm) in non-insulin - resistant obese women. The frequency of endometrial thickness over 5.0 mm was 78.57% in insulin- resistant obese women and 36.36% in noninsulin - resistant obese women.* ***Conclusion:*** *In postmenopausal women central obesity, high endogenous estrogen levels and insulin resistance were associated with increased endometrial thickness, a risk indicator of uterine (endometrial) cancer.*
Keywords: *endometrial thickness, postmenopausal women, insulin resistance*

Introduction

The endometrium functions as a lining for the uterus that prevents adhesions between the opposed walls of the myometrium, thereby maintaining the patency of the uterine cavity. The endometrium consists of a single layer of columnar epithelium, resting on a layer of connective tissue - the stroma - which varies in thickness according to hormonal influences.

Postmenopause the endometrium is often described as being atrophic. During this time, estrogen, progesterone and ovarian androgens are diminished due to adult-onset ovarian failure. Estrone (E1)

is the dominant form of estrogen during menopause. It is produced in small quantities by the ovary and the adrenal glands, and is principally derived by the peripheral conversion of androstenedione in adipose tissue.

Obesity has been consistently associated with uterine (endometrial) cancer[1,2]. It is unclear why obesity is a risk factor for endometrial cancer; however, it has been suggested that lifetime exposure to hormones and high levels of estrogen and insulin in obese women may be contributing factors.

The principal mechanism by which hormones and growth factors are thought to influence cancer risk is their regulatory effect on cell proliferation, differentiation, and apoptosis. Increased proliferation rates raise the probability that mutations accumulate in proto-oncogenes and tumor suppressor genes[3,4,5,6]. Impairment of apoptosis may allow cells that have harbored such mutations to survive and eventually to expand clonally, thus allowing them to accumulate additional mutations until full malignancy is reached. The differentiation of cells and maintenance of cells in a differentiated state, are thought to protect against tumor development, because highly differentiated cells have reduced proliferative potential[7,8].

Estrogens

The predominant theory describing the relationship between endogenous steroid hormones and endometrial cancer risk is known as the unopposed estrogen hypothesis[3]. This hypothesis proposes that endometrial cancer risk is increased in women who have high plasma bioavailable estrogens and/or low plasma progesterone, so that mitogenic effects of estrogens on endometrium are insufficiently counterbalanced by progesterone.

Insulin

Epidemiological studies have consistently shown an increased risk of endometrial cancer in both pre- and postmenopausal women with noninsulin-dependent diabetes[9], a disease that is preceded by many years of increasing insulin resistance, elevated fasting and nonfasting plasma insulin, and which generally remains associated with hyperinsulinemia for many years even after diagnosis. A number of mechanisms may link elevated insulin to endometrial cancer development. There is evidence that insulin can act as a growth factor, with effects similar to those of insulin like growth factor I (IGF-I). Tumor tissues, including endometrial tumors, generally have increased expression of IGF-I receptors[10,11], and increased insulin receptor expression has also been reported[12]. Elevated insulin increases IGF-I activity in endometrial tissue by suppressing gene expression of endometrial insulin-like growth factor binding protein-1 (IGFBP-1) [13]. Experiments *in vitro* have indeed shown that insulin is a key regulator of IGFBP-1 gene expression and its production in the liver[14], and that it may also reduce IGFBP-1 synthesis in other tissue types, including endometrium[15]. Insulin stimulates ovarian (and possibly also adrenal) androgen synthesis, too. Insulin is a key regulator of the hepatic synthesis and plasma levels of sex-hormone binding globuline (SHBG), down-regulating SHBG levels, and is thus a direct determinant of bioavailable 17 beta-estradiol (E_2) unbound to SHBG[16].

Aim

To evaluate the correlation between endometrial thickness and insulin and estrogen levels in postmenopausal obese women

Materials and Methods

A pilot study was used. The sample was composed of 14 postmenopausal insulin-resistant obese women and 11 postmenopausal non insulin- resistant obese women The women did not use hormone replacement therapy. The hepatic, renal and hematological severe pathology where considered as exclusion criterion from the study. The anthropometric measurement included waist circumference (WC) and body mass index (BMI). BMI was computed as a ratio of weight to the square of height (kg/m^2). Waist circumference was taken at the midpoint between the lowest rib and the iliac crest. Obesity is defined as a body mass index of 30 kg/m^2 or higher. The waist circumference > 88 cm in women is used as a threshold of central obesity. Estimates of insulin resistance were derived from the HOMA index[17] - Homeostasis model assessment: basal glucose mmol/l x basal insulin μIU/ml/22.5; insulin-resistant women were defined by HOMA >3. Blood samples were drawn the morning after an overnight fast. Serum insulin, glucose, estrone were measured. The women have normal glucose tolerance by the criteria of the World Health Organization. Real-time ultrasonography was done with a 5 MHz vaginal transducer. With the uterus imaged in the longitudinal plan, endometrial thickness was measured at the thickest point between the two basal layers on the anterior and posterior uterine walls.

Results

BMI ranged from 30.24 kg/m^2 to 36.48 kg/m^2 (median value 32.12 kg/m^2) in insulin- resistant obese women and 30.42 kg/m^2 to 36.56 kg/m^2 (median value 32.68 kg/m^2) in noninsulin-resistant obese women. Waist circumference ranged from 93 cm to 102 cm (median value 101.5 cm) in insulin-resistant women (central obesity is present in 11 women - 78.57%) and 84 cm to 100 cm (median value 88.0 cm) in noninsulin- resistant women (central obesity is present in 3 women - 27.27%). Estrone ranged from 28 pg/ml to 36 pg/ml (median value 32 pg/ml) in insulin-resistant obese women and 28 pg/ml to 34 pg/ml (median value 28 pg/ml) in noninsulin-resistant obese women. En-

dometrial thickness measurements ranged from 5 to 20 mm (median 6.00 mm) in insulin-resistant obese women and 4 to 8 mm (median 4.00 mm) in noninsulin-resistant obese women. The frequency of endometrial thickness over 5.0 mm was 78.57% in insulin-resistant obese women and 36.36% in noninsulin-resistant obese women. The frequency of endometrial thickness over 5.0 mm, was 85. 71% in women with central obesity (6 insulin-resistant obese women and 1 noninsulino-resistant obese woman).

Statistical analysis

For the statistical analysis of the results The Program SPSS 9.0 was used. For the data processing where selected a non-parametric test (Mann Whitney U). The statistical significance was accordingly to a p value < 0.05.

Discussions

The normal postmenopausal endometrium should appear thin, homogeneous, and echogenic. There is controversy regarding endometrial thickness with menopause. In general, a double-layer thickness of less than 5 mm without focal thickening excludes significant disease and is consistent with atrophy[18]. Homogeneous, smooth endometrium measuring 5 mm or less are considered within the normal range with or without hormonal replacement therapy[18]. Transvaginal ultrasonography has been proposed to be the test of first choice in postmenopausal women with vaginal bleeding because of its almost perfect accuracy[19]. Because of the fact that the probability of malignancy is strongly reduced in case of an endometrial thickness of 5 mm or less, follow-up management may be justified in women with such test results.

Obesity has been consistently associated with uterine (endometrial) cancer. It is unclear why obesity is a risk factor for endometrial cancer. However, it has been suggested that lifetime exposure to hormones and high levels of estrogen and insulin in obese women may be contributing factors.

Most cases of endometrial hyperplasia result from high levels of estrogens, combined with insufficient levels of the progesterone-like hormones which ordinarily counteract estrogen's proliferative effects on this tissue. Like other hyperplastic disorders, endometrial hyperplasia initially represents a physiological response of endometrial tissue to the growth-promoting actions of estrogen[20].

The obtained results are in agreed with the literature data. The thickness of the endometrium at the insulinoresistance patients group was significantly higher than the obese group, without insulinoresistance (7.21 ± 4.30mm vs 5.00 ± 1.34, p = 0,022). These results are correlated with a significant growth of the estrone concentration at the pacients with insulinoresistance comparing with the noninsulinoresistance group (31.42 ± 2.27 mg/dl vs. 28.90 ± 2.73 mg/dl, p = 0.023).

The present study obtained results illustrate the fact that the group with insulinoresistance is characterized by a HOMA Index (4.02 ± 0.70), and a waist circumference (100.92 ± 4.19 cm) significantly higher comparing with the group without insulinoresistance (HOMA Index 2.80 ± 0.17, waist circumference 90.54 ± 6.51).

Increased levels of insulin bind to IGF1 (*insulin-like growth factor I*) receptor that resemble with insulin receptor and signals through tyrozin kinase activation. Activation of IGF1 receptors in the endometrium increases proliferation and the risk of neoplasia[12].

Conclusion

In postmenopausal women central obesity, high endogenous estrogen levels and insulin resistance were associated with increased endometrial thickness, a risk indicator of uterine (endometrial) cancer. ■

Bibliografie

1. Weight control and physical activity. In: H. Vaino and F. Bianchini (eds), IARC Handbook for Cancer Prevention Vol. 6, pp. 1–315. Lyon, France: IARC Press, 2002.
2. Bergstrom A., Pisani P., Tenet V., Wolk A., Adami H. O. Overweight as an avoidable cause of cancer in Europe. Int. J. Cancer, 91: 421-430, 2001.
3. Kaaks R., Lukanova A., Kurzer S. M., Obesity, Endogenous Hormones and Endometrial Cancer Risk, Cancer Epidemiology Biomarkers & Prevention Vol. 11, 1531-1543, 2002.
4. Ames B. N., Shigenaga M. K., Gold L. S. DNA lesions, inducible DNA repair, and cell division: three key factors in mutagenesis and carcinogenesis. Environ. Health Perspect., 101 (Suppl. 5): 35-44, 1993.
5. Cohen S. M., Ellwein L. B. Genetic errors, cell proliferation, and carcinogenesis. Cancer Res., 51: 6493-6505, 1991.
6. Ames B. N., Gold L. S. Too many rodent carcinogens: mitogenesis increases mutagenesis. Science (Wash. DC), 249: 970-971, 1990.
7. Preston-Martin S., Pike M. C., Ross R. K., Jones P. A., Henderson B. E. Increased cell division as a cause of human cancer. Cancer Res., 50: 7415-7421, 1990.
8. Cory S., Vaux D. L., Strasser A., Harris A. W., Adams J. M. Insights from Bcl-2 and Myc: malignancy involves abrogation of apoptosis as well as sustained proliferation. Cancer Res., 59: 1685s-1692s, 1999.
9. La V. C., Negri E., Franceschi S., D'Avanzo B., Boyle P. A case-control study of diabetes mellitus and cancer risk. Br. J. Cancer, 70: 950-953, 1994.
10. Talavera F., Reynolds R. K., Roberts J. A., Menon K. M. Insulin-like growth factor I receptors in normal and

Bibliografie

neoplastic human endometrium. Cancer Res., 50: 3019-3024, 1990.
11. Nagamani M., Stuart C. A. Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture. Am. J. Obstet. Gynecol., 179: 6-12, 1998.
12. Irwin J. C., de las F. L., Dsupin B. A., Giudice L. C. Insulin-like growth factor regulation of human endometrial stromal cell function: coordinate effects on insulin-like growth factor binding protein-1, cell proliferation and prolactin secretion. Regul. Pept., 48: 165-177, 1993.
13. Rechler M. M. Insulin-like growth factor binding proteins. Vitam. Horm., 47: 1-114, 1993.
14. Lee P. D., Giudice L. C., Conover C. A., Powell D. R. Insulin-like growth factor binding protein-1: recent findings and new directions. Proc. Soc. Exp. Biol. Med., 216: 319-357, 1997.
15. Franks S., Kiddy D. S., Hamilton-Fairley D., Bush A., Sharp P. S., Reed M. J. The role of nutrition and insulin in the regulation of sex hormone binding globulin. J. Steroid Biochem. Mol. Biol., 39: 835-838, 1991.
16. Plymate S. R., Matej L. A., Jones R. E., Friedl K. E. Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. J. Clin. Endocrinol. Metab., 67: 460-464, 1988.
17. Matthews D.R., Hosker J.P., Rudenski A. S., Naylor B. A., Treacher D.F., Turner R.C.,- Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentration in man. Diabetologia 1985, 28: 412-419.
18. Goldstein SR, Nachtigall M, Snyder JR, et al. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. Am J Obstet Gynecol 1990; 163:119-123.
19. Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA 1998; 280:1510–7.
20. Richard Cote, Saul Suster, Lawrence Weiss, Noel Weidner (Editor) . Modern Surgical Pathology (2 Volume Set). 2002, London: W B Saunders.