Serum adiponectin in relation to endometrial cancer and endometrial hyperplasia with atypia in obese women

I. Rzepka-Górska, R. Bedner, A. Cymbaluk-Płoska, A. Chudecka-Głaz

Department of Gynecological Surgery and Oncology of Adults and Adolescents, Pomeranian Medical University of Szczecin (Poland)

Summary

Objectives: The aim of this work was to compare concentrations of adiponectin in the serum of obese women with endometrial cancer, endometrial hyperplasia with atypia, and normal endometrium. *Methods:* We enrolled 105 obese women treated at the Department of Gynecological Surgery and Oncology of Adults and Adolescents. The patients were allocated to groups depending on the histological diagnosis (R - endometrial cancer, P - polyps, K - normal endometrium). We subdivided group R depending on the stage and grade of cancer. *Results:* Significantly lower concentrations of adiponectin were found in patients with endometrial cancer (mean 15.28 μg/ml) as compared with polyps (29.94 μg/ml, $p < 0.001$) or normal endometrium (22.7 μg/ml, $p < 0.05$). Stage of cancer had no significant effect on the adiponectin level. When cancer grade was compared, lower levels of adiponectin were observed in patients with G3 (12.86 μg/ml) than G1 (19.04 μg/ml, $p < 0.05$). *Conclusion:* Reduced levels of adiponectin may represent an independent risk factor for endometrial cancer

Key words: Endometrial cancer; Endometrial hyperplasia; Adiponectine; Obesity.

Introduction

It is presently known that adipose tissue, besides storing energy, actively modulates metabolic processes and participates in energy metabolism of such vital organs as the brain, muscles (heart), and liver. To play its metabolic role, adipose tissue is the source of several substances possessing unquestionable physiologic significance [1]. Some of them, including leptin, adiponectin, angiotensinogen, resistin, and estrogens, have endocrine properties. Other substances, like tumor necrosis factor-α (TNF-α) and insulin-like growth factor (IGF-1), exert paracrine action.

Adiponectin is produced exclusively in adipose tissue. Interest in this adipocytokine has grown after it was shown that hypoadiponectinemia is associated with metabolic syndrome, overweight, obesity, type 2 diabetes, insulin resistance, hyperlipoproteinemia, and some neoplasms [2-8]. A five-year study by Chow et al. [9] has demonstrated that reduced adiponectin levels in blood are associated with arterial hypertension. As hypoadiponectinemia precedes progression to hyperglycemia, this cytokine has been termed by some as a biomarker of metabolic disease [9]. On the other hand, high concentrations of adiponectin appear to exert a protective effect on the cardiovascular system [10-12]. Hyperadiponectinemia seems to be of benefit for energy homeostasis of the organism in cases of anorexia nervosa [13].

Endometrial cancer is a hormone-associated and estrogen-dependent neoplasm usually diagnosed in women continuously exposed to estrogens not followed by gestagenic action. In postmenopausal women, estrogens are produced during steroidogenesis in the reticular layer of the adrenals. Androstendione is the substrate for estrone, the chief postmenopausal female hormone. The same metabolic process of aromatization serves to produce estradiol from testosterone. Obesity, hypertension, diabetes, and androgenic syndromes in women, particularly polycystic ovary syndrome, are the main risk factors of endometrial cancer.

This work was undertaken: (1) to determine serum concentrations of adiponectin in obese women with endometrial cancer, endometrial hyperplasia with atypia, endometrial polyps, and normal controls; (2) to determine serum concentrations of adiponectin in obese women with endometrial cancer depending on the presence of other risk factors – arterial hypertension or type 2 diabetes (three risk factors); and (3) to determine serum concentrations of adiponectin depending on the stage and grade of endometrial cancer.

Material and Methods

We studied 105 obese women admitted to our department for hysterectomy for different reasons. The patients were divided in three basic groups: R - with endometrial cancer and endometrial hyperplasia with atypia, P- with endometrial polyps, and K- with normal endometrium.

Three other subgroups were created depending on risk factors of endometrial cancer: B1 - obesity + hypertension + diabetes (n = 21), B2 - obesity + hypertension (n = 46), and B3 - obesity only (n = 27). Staging and grading of the endometrial cancer was done postoperatively in all cases of the tumor (n = 34). The control group (K) consisted of obese women with normal endometrium. All participants provided their written informed consent to participate in the study. The study protocol was approved by the local bioethics committee.

Adiponectin concentrations were determined at the laboratory of the Department of Endocrinology, Arterial Hypertension

Revised manuscript accepted for publication March 20, 2008

and Metabolic Diseases, Pomeranian Medical University, using radioimmunoassay kits from R&D. Sensitivity was 1 ng/ml and inter-series repeatability was 1.8-6.2% .

Results

Mean concentrations of adiponectin in the serum of patients with endometrial cancer and hyperplasia with atypia (n = 37) was 15.28 μg/ml (3.7-26.5 μg/ml) as compared with 22.7 μg/ml (8.9-59.2 μg/ml) in controls (n = 68) ($p < 0.001$, Table 1). Adiponectin concentrations in women with endometrial polyps (n = 20) was 29.94 μg/ml (14.1-38.0 μg/ml) ($p < 0.001$ as compared with endometrial cancer, Table 2). The difference in adiponectin levels between patients with endometrial polyps and controls was not significant (Table 3).

Table 1. — *Concentrations of adiponectin in the serum of obese women (group R and group K).*

Group	Adiponectin μg/ml		
	R (n = 37)	p	K (n = 48)
Mean	15.28		22.7
Range	3.7-26.5	< 0.05	8.9-59.2
Median	15.3		19.2
Confidence interval	13.1-17.5		16.9-28.5
Standard deviation	5.74		13.37

Group R - patients with endometrial cancer or endometrial hyperplasia with atypia; Group K - patients with normal endometrium; p - statistical significance; N - number of patients.

Table 2. — *Concentrations of adiponectin in the serum of obese women (group R and group P).*

Group	Adiponectin μg/ml		
	R (n = 37)	p	K (n = 20)
Mean	15.28		29.94
Range	3.7-26.5	< 0.001	14.1-38.0
Median	15.3		23.2
Confidence interval	13.1-17.5		20.6-29.3
Standard deviation	5.74		7.79

Group R - patients with endometrial cancer or endometrial hyperplasia with atypia; Group P - patients with endometrium polyps; p - statistical significance; N - number of patients.

Table 3. — *Concentrations of adiponectin in the serum of obese women (group P and group K).*

Group	Adiponectin μg/ml		
	R (n = 20)	p	K (n = 20)
Mean	29.94		22.7
Range	14.1-38	NS	8.9-59.2
Median	23.2		19.2
Confidence interval	20.6-29.3		16.9-28.5
Standard deviation	7.79		13.37

Group P - patients with endometrium polyps; Group K - patients with normal endometrium; p - statistical significance (NS - not significant); N - number of patients.

We next compared adiponectin levels depending on the presence of risk factors of endometrial cancer. Mean concentrations in the B1 subgroup was 14.41 μg/ml (7.9-22.1 μg/ml) for patients with endometrial cancer and hyperplasia with atypia, as compared with 23.3 μg/ml (17.3-29.2 μg/ml) in controls ($p < 0.001$, Table 4). For two risk factors (B2), the results were 15.78 μg/ml (3.7-22.2 μg/ml) versus 22.87 μg/ml (13.2-28.1 μg/ml) in controls ($p < 0.001$, Table 5). When only obesity was present (B3), adiponectin levels were 15.9 μg/ml (9.4-26.5 μg/ml) in patients with endometrial cancer and hyperplasia with atypia as compared with 27.8 μg/ml (9.4-56.1 μg/ml) in controls ($p < 0.001$, Table 6).

Table 4. — *Concentrations of adiponectin in the serum of group R and group K with three risk factors for endometrial cancer (B1).*

Group	Adiponectin μg/ml		
	R (n = 12)	p	K (n = 9)
Mean	14.41		23.3
Range	7.9-22.1	< 0.001	17.3-29.2
Median	13.7		23.2
Confidence interval	10.39-18.43		8.45-38.01
Standard deviation	5.98		5.95

Group R - patients with endometrium cancer or endometrial hyperplasia with atypia; Group K - patients with normal endometrium; p - statistical significance; N - number of patients.

Table 5. — *Concentrations of adiponectin in the serum of group R and group K with two risk factors for endometrial cancer (B2).*

Group	Adiponectin μg/ml		
	R (n = 22)	p	K (n = 24)
Mean	15.78		22.87
Range	3.7-22.2		13.2-28.1
Median	16.1	< 0.001	19.65
Confidence interval	12.34-19.21		7.9-21.8
Standard deviation	5.69		12.69

Group R - patients with endometrium cancer or endometrial hyperplasia with atypia; Group K - patients with normal endometrium; p - statistical significance; N - number of patients.

Table 6. — *Concentrations of adiponectin in the serum of group R and group K with one risk factor for endometrial cancer (B1).*

Group	Adiponectin μg/ml		
	R (n = 5)	p	K (n = 22)
Mean	15.9		27.8
Range	9.4-26.5		9.4-56.1
Median	14.1	< 0.001	23
Confidence interval	8-23.8		4.06-59.81
Standard deviation	6.36		20.07

Group R - patients with endometrium cancer or endometrial hyperplasia with atypia; Group K - patients with normal endometrium; p - statistical significance; N - number of patients.

The mean adiponectin level in Stage 3 and 4 endometrial cancer was 14.97 μg/ml (3.7-36.8 μg/ml) and did not differ significantly from 15.4 μg/ml (13.9-20.2 μg/ml) in Stage 1 (Table 7). Patients with grade 1 tumor (n = 12) demonstrated a mean adiponectin concentration of 19.04 μg/ml (3.7-36.8 μg/ml), as compared with 13.48 μg/ml (7.9-26.1 μg/ml) in patients with G2 (n = 13) and 12.86 μg/ml (10.8-14.0 μg/ml) in patients with grade 3 (n = 8). The difference between G1 and G3 was significant ($p < 0.05$, Table 8), whereas the difference between G1 and G2 was not (Table 9).

Discussion

It is believed that obesity in some way favors neoplastic transformation in the endometrium. The adipose tissue is the site of peripheral aromatization of adrenal

Table 7. — *Concentrations of adiponectin in the serum of patients with endometrial cancer depending on stage.*

Group	Adiponectin µg/ml		
	1 (n = 28)	p	3 + 4 (n = 5)
Mean	15.4		14.97
Range	13.9-20.2		3.7-36.8
Median	15.3	NS	13.7
Confidence interval	12.42-20.7		9.89-21.32
Standard deviation	2.62		8.19

1, 3, 4 - stage of endometrial cancer; 1 - includes stages 1a, 1b, and 1c; p - statistical significance (NS - not significant); N - number of patients.

Table 8. — *Concentrations of adiponectin in the serum of patients with endometrial cancer depending on grade.*

Group	Adiponectin µg/ml		
	G1 (n = 12)	p	G3 (n = 8)
Mean	19.04		12.86
Range	3.7-36.8		10.8-14.0
Median	18.85	< 0.05	12.9
Confidence interval	11.1-26.9		11.3-14.4
Standard deviation	9.43		1.25

G1, G3 - grade of histological differentiation of endometrial cancer; p - statistical significance; N - number of patients.

Table 9. — *Concentrations of adiponectin in the serum of patients with endometrial cancer depending on grade.*

Group	Adiponectin µg/ml		
	G1 (n = 12)	p	G2 (n = 13)
Mean	19.04		13.48
Range	3.7-36.8		7.9-26.1
Median	18.85	NS	12.0
Confidence interval	11.1-26.9		9.89-17.1
Standard deviation	9.43		5.95

G1, G2 - grade of histological differentiation of endometrial cancer; p - statistical significance (NS - not significant); N - number of patients.

androstenedione to estrone. Elevated levels of endogenous estrogens stimulate the proliferation of endometrial cells. Insulin resistance also contributes to enhanced proliferation due to the direct binding of insulin with its receptors on endometrial cells [14].

Adiponectin is a hormone with anti-diabetic, anti-atherosclerotic, anti-inflammatory, and anti-tumor action, produced by adipose tissue [4, 6, 13,15]. We have now shown that obese patients with endometrial cancer or hyperplasia with atypia have significantly lower levels of this adipocytokine than obese patients with a normal endometrium ($p < 0.05$). Levels in patients with endometrial cancer were lower than in endometrial polyps ($p < 0.001$). Similar findings were reported by Soliman et al. [16] for patients with endometrial cancer (88.8 ± 63.3 ng/ml, n = 117) as compared with normal controls (148.2 ± 68.3 ng/ml, n = 238; $p < 0.01$). Moreover, the risk of endometrial cancer in that study was greatest for patients with the lowest levels of adiponectin. Although subgrouping according to tumor stage and grade was done by these researchers, adiponectin levels per stage or grade were not published.

In our study, patients with normal BMI values (< 25 kg/m^2) were at greatest risk of endometrial cancer when adiponectin levels were at their lowest (12.9-112.2 ng/ml, $p = 0.002$). Our interpretation of this finding is that hypoadiponectinemia is a risk factor for endometrial cancer independently of BMI. Similar data were provided by Cust *et al.* [17], Dal Maso et al. [18], and Petridou *et al.* [19]. Dal Maso and colleagues [18] reported lower values of adiponectinemia in patients with endometrial cancer (mean 11.4, range 6.5-17.1 µg/ml) as compared with controls (mean 16.0, range 8.4-22.5 µg/ml). Petridou *et al.* [19] found that an increase of one standard deviation in adiponectin concentration reduced the risk of endometrial cancer by 50%.

A pan-European study in 135,953 women published in 2007 clearly demonstrated a link between adiponectin levels and endometrial cancer [17]. This tumor was diagnosed in 284 patients after a mean follow-up of 5.1 years. Cust *et al.* [17] reported that adiponectin levels in endometrial cancer were 15% lower than in normal controls. Moreover, rising adiponectin concentrations were associated with decreasing risk of endometrial cancer. This beneficial effect of adiponectin was largely independent of concentrations of other risk factors associated with obesity, such as peptide C, IGFBP-1, IGFBP-2, SHBG, estrone, and testosterone.

In the present study, adiponectin levels were higher in G1 as compared with G3 tumors ($p < 0.05$). We are tempted to relate this finding to the report of Takemura *et al.* [20] who found both isoforms of the adiponectin receptor (AdipoR1 and AdipoR2) on epithelial cells and cells of the endometrial matrix, and interpreted this finding in support of the direct action of adiponectin on the endometrium.

The present findings and those reported by others [16, 17] are in agreement with a protective action of adiponectin against endometrial cancer. Possible mechanisms of adiponectin activity could involve enhancement of fatty acid oxidation in skeletal muscles, suppression of hepatic gluconeogenesis, facilitation of insulin signaling transduction, or promotion of insulin sensitivity in peripheral tissues [21, 22].

Acknowledgment

This study was supported by a grant from the State Committee for Scientific Research.

References

[1] Fruhbeck G., Gomez-Ambrozi J., Muruzaba F.J., Burrel M.A.: "The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation". *Am. J. Physiol. Endocrinol. Metabol.,* 2001, *280,* E827.

[2] Gannage-Yared M.H., Khalife S., Semaan M., Fares F., Jambart S., Halaby G.: "Serum adiponectin and leptin levels in relation to the metabolic syndrome, androgenic profile and somatotropic axis in healthy non-diabetic elderly men". *Eur. J. Endocrinol.,* 2006, *155,* 167.

[3] Tataranni P.A., Ortega E.: "A burning question: does an adipokine-induced activation of the immune system mediate the effect of the overnutrition on type 2 diabetes"? *Diabetes,* 2005*, 54*, 917.

[4] Kelesidis I., Kelesidis T., Mantzoros C.S.: "Adiponectin and cancer: a systematic review". *Br. J. Cancer*, 2006, *94*, 1221.

[5] Lara-Castro C., Fu Y., Chung B.H., Garvey W.T.: "Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease". *Curr. Op. Lipidol.*, 2007, *18,* 263.

[6] Weyer C., Funahashi T., Tanaka S., Hotta K., Matsuzawa Y., Pratley R.E.: "Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia". *J . Clin. Endocrinol. Metabol.,* 2001, *86*, 1930.
[7] Cong L., Gasser J., Zhao J., Yang B., Li F., Zhao A.Z.: " Human adiponectine inhibits cell growth and induces apoptosis in human endometrial carcinoma cells, HEC-1-A and RL 952". *Endocr. Relat. Cancer*, 2007, *14,* 713.
[8] Vona-Davis L., Rose D.P.: "Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression". *Endocr. Relat. Cancer*, 2007, *14,* 189.
[9] Chow W.S., Cheung B.M., Tso A.W., Xu A., Wat N.M., Fong C.H. *et al.*: "Hypoadiponectinemia as a predictor for the development of hypertension. A 5-year prospective study". *Hypertension,* 2007*, 49,* 1455.
[10] Brooks N.L., Moore K.S., Clark R.D., Perfetti M.T., Trent C.M., Combs T.P.: "Do low levels of circulating adiponectin represent a biomarker or just another risk factor for the metabolic syndrome?". *Diabet. Obstet. Metabol.,* 2007, *9,* 246.
[11] Ouchi N., Shibata R., Walsh K.: "Targeting adiponectin for cardioprotection". *Exp. Opin. Ther. Targets*, 2006, *10,* 573.
[12] Trujillo M.E., Scherer P.E.: "Adiponectin-journey from an adipocyte secretory protein to biomarker of the metabolic syndrome". *J. Int. Med.*, 2005, *257*, 167.
[13] Modan-Moses D., Stein D., Pariente C., Yaroslavsky A., Ram A., Faigin M. *et al.*: "Modulation of adiponectin and leptin during refeeding of female anorexia nervosa patients". *J. Clin. Endocrinol. Metabol.,* 2007, *92*, 1843.
[14] Nagamani M., Stuart C.A.: "Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture". *Am. J. Obstet. Gynecol.,* 1998, *179*, 6.
[15] Korner A., Kratzsch J., Gausche R., Schaab M., Erbs S., Kiess W.: "New predictors of the metabolic syndrome in children - role of adipocytokines". *Pediatr. Res*., 2007, *61*, 640.
[16] Soliman P.T., Wu D., Tortolero-Luna G., Schmeler K.M.: "Association between adiponectin, insulin resistance, and endometrial cancer". *Cancer*, 2006, *106,* 2376.
[17] Cust A.E., Kaaks R., Friedenreich C., Bonnet F., Laville M., Lukanova A. *et al.*: "Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women". *J. Clin. Endocrinol. Metabol.,* 2007, *92,* 255.
[18] Dal Maso L., Augustin L.S., Karalis A.: "Circulating adiponectin and endometrial cancer risk". *J. Clin. Endocrinol. Metabol.,* 2004, *89,* 1160-3.
[19] Petridou E., Mantzoros C., Dessypris N.: "Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece". *J. Clin. Endocrinol. Metabol.*, 2003, *88,* 993.
[20] Takemura Y., Osuga Y., Yamauchi T.: "Expression of adiponectin receptors and its possible implication in the human endometrium". *Endocrinol.*, 2006, *147,* 3203.
[21] Fu Y., Luo N., Klein R.L., Garvey W.T.: "Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation". *J. Lipidol. Res.*, 2005, *46*, 1369.
[22] Lihn A.S., Pedersen S.B., Richelsen B.: "Adiponectin: action, regulation and association to insulin sensitivity". *Obstet. Rev.,* 2005, *6,* 3.

Address reprint requests to:
I. RZEPKA-GÓRSKA, M.D.
Ul. Powstańców Wielkopolskich 72
70-111 Szczecin (Poland)
e-mail : IzGorska@sci.pam.szczecin.pl