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Comparison of asprosin immunoreactivity in endometrial hyperplasia and grade-1 endometrial adenocarcinoma: A retrospective case-control study

Endometriyal hiperplazi ve grade-1 endometriyal adenokarsinomdaki asprosin immünoreaktivitesinin karşılaştırılması: Retrospektif bir olgu-kontrol çalışması

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Abstract

Objective: It has been demonstrated that asprosin, a glucogenic adipokine released by white adipose tissue, contributes to the pathophysiology of cancer and disorders associated with it. The aim of this study was to compare the immunoreactivity of asprosin in grade I endometrial adenocarcinoma and in endometrial hyperplasia (EH) with and without atypia.

Materials and Methods: A total of 80 cases previously diagnosed with grade 1 endometrial adenocarcinoma and EH with and without atypia, and for which paraffin blocks were obtained, were included in the study. The resulting paraffin blocks were sectioned again and immunostained for asprosin. A total of 80 cases were divided into 4 groups according to their histopathological diagnoses. Group (G) 1 (n=20): proliferative endometrium, G2 (n=20): EH without atypia, G3 (n=20): EH with atypia, G4 (n=20): Grade 1 endometrial adenocarcinoma. Endometrial samples from 80 patients were sectioned, and asprosin immunoreactivity was evaluated by immunohistochemical staining under a light microscope.

Results: In comparison to the proliferative endometrium group, the grade I endometrial adenocarcinoma group had considerably increased asprosin immunoreactivity. However, between the proliferative endometrium group and the groups with endometrial hyperplasia, without atypia, and endometrial hyperplasia, with atypia, there was no significant difference in asprosin immunoreactivity.

Conclusion: While asprosin immunoreactivity scores are higher in grade I endometrial adenocarcinomas, they are similar to those of the proliferative endometrium in cases of EH with and without atypia, suggesting that energy metabolism contributes to the development of cancer arising from endometrial hyperplasia. Asprosin immunoreactivity can be studied as a marker to predict the progression of EH to cancer.

Keywords: Immunohistochemistry, asprosin, endometrial hypeplasia, endometrial cancer

PRECIS: Asprosin may play a role in the pathogenesis of endometrial hyperplasia.

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Öz

Amaç: Beyaz yağ dokusundan salgılanan glukojenik bir adipokin olan asprosinin, kanser ve ilişkili bozuklukların patofizyolojisine katkıda bulunduğu gösterilmiştir. Bu çalışmanın amacı, atipili ve atipisiz endometriyal hiperplazi ve grade 1 endometriyal adenokarsinomda asprosinin immünoreaktivitesini karşılaştırmaktır.

Gereç ve Yöntemler: Çalışmaya daha önceden grade 1 endometriyal adenokarsinom ile atipisiz ve atipili endometriyal hiperplazi (EH) tanısı almış ve parafin blokları elde edilen toplam 80 olgu dahil edildi. Elde edilen parafin bloklardan tekrar kesitler alınarak asprosin için immünboyama yapıldı. Toplam 80 olgu histopatolojik tanılarına göre 4 gruba ayrıldı. Grup (G) 1 (n=20): proliferatif endometriyum, G2 (n=20): atipisiz EH, G3 (n=20): atipili EH, G4 (n=20): Evre 1 endometriyal adenokarsinom. Seksen hastadan alınan endometriyal örnekler tekrar kesitlendirildi ve asprosinin immünoreaktivitesi ışık mikroskobu altında immünhistokimyasal boyama ile değerlendirildi.

Bulgular: Proliferatif endometriyum grubuyla karşılaştırıldığında, evre I endometriyal adenokarsinom grubunda asprosin immünoreaktivitesi anlamlı olarak artmıştı. Ancak, proliferatif endometriyum grubu ile atipisiz EH ve atipili EH grupları arasında asprosin immünoreaktivitesi açısından anlamlı bir fark yoktu.

Sonuç: Asprosin immünoreaktive skorlarının grade I endometriyal adenokarsinomlarda yüksek olmasına karşın atipisiz ve atipili EH'lerde proliferatif endometriyuma benzer şekilde olması enerji metabolizmasının EH'den kaynaklanan kanser gelişimine katkıda bulunduğunu göstermektedir. Asprosin immünreaktivitesi EH'den kansere dönüşümü tahmin etmede bir belirteç olarak incelenebilir.

Anahtar Kelimeler: İmmünohistokimya, asprosin, endometriyal hipeplazi, endometriyal kanser

Introduction

The abnormal growth of endometrial glands brought on by a relative lack of progesterone and prolonged exposure to estrogen, is known as endometrial hyperplasia (EH)[1]. Histopathological complexity, unusual features, an aberrant gland-to-stroma ratio, and uneven endometrial growth are its defining characteristics. It should be mentioned, though, that untreated cases of EH might result in the development of endometrial cancer (EC)[1-3]. In 2014, the World Health Organization divided EHs into two groups based on whether they had cytological atypia. In this instance, cases with atypia were categorized as endometrial intraepithelial neoplasia, whereas those without atypia were classified as EH[4].

Although the risk of EC is about quadrupled in cases of hyperplasia without atypia, curettage and hormonal therapy are effective in the majority of cases[5]. Since EH is a precursor lesion to EC and has an incidence that is almost three times higher than EC, early diagnosis can prevent the progression to cancer[6]. The transition from hyperplasia without atypia to hyperplasia with atypia and carcinoma is the first stage of endometrial endometrioid cancer. It has been proposed that unopposed estrogen signaling is a key factor in the initiation of EH and its progression to endometrial endometrioid cancer[7]. EC has an overall five-year survival rate of 81% and a 3.1% lifetime risk[8]. Fortunately, because of the early signs of postmenopausal bleeding, the disease is typically limited to the uterus, with a median diagnostic age of 64. Five-year survival rates are 95% when localized disease is found and surgically removed. Five-year survival rates for distant organ disease, however, are only 18%. Medical therapy, radiation therapy, and surgery are the three main methods of treating endometrial cancer[7]. It is projected that in 2023, there will be 13,030 uterine cancer-related fatalities and 66,200 new cases in the United States[9]. These global and national patterns have several underlying causes that are not well understood. Estrogen-related risk factors, including obesity, nulliparity, late menopause, early menarche, and estrogen supplementation during menopause, are linked to almost 80% of endometrial cancers, which are estrogen receptor positive[10].

In certain nations undergoing socioeconomic transition, the rapidly rising incidence of EC may be attributed to changes in fertility and reproductive variables, such as fewer pregnancies and nulliparity. Furthermore, obesity is on the rise globally and is likely a factor in this development. Additional variables to take into account include shifts in the use of perimenopausal hormones, increases in diabetes, declines in smoking incidence, modifications to birth control, and shifts in the rates of hysterectomy[11]. It has been demonstrated that adipose tissue and fat cells contribute to tumor growth and progression[12-14]. White adipose tissue secretes the glucogenic adipokine asprosin, which controls blood sugar levels. The G protein-cAMP-PKA pathway is activated by asprosin, causing the release of glucose into the circulation[15]. Asprosin is mostly found in white adipose tissue, although it is also present in the lung, heart, liver, skeletal muscle, and pancreas[15,16]. Furthermore, it has been demonstrated that asprosin levels are altered in cancer and illnesses that may be linked to cancer[13,17]. Our study's objectives were to investigate asprosin immunoreactivity in patients with grade 1 endometrioid adenocarcinoma, proliferative endometrium, and EH with or without atypia.

Materials and Methods

This retrospective case-control study was approved by the ethical committee and carried out in compliance with the Declaration of Helsinki's principles.

Selection of Cases

Ethical approval was obtained from the Fırat University Non-Interventional Research Ethics Board (date: 13.01.2022, number: 2022/01-07). Endometrium samples (biopsies and resections) obtained between 2010 and 2020 were retrospectively scanned in the archive of the university department of pathology. Once pathology reports were reviewed and previous pathological diagnoses were confirmed, a total of 80 patients were included in the study, with 20 cases in each group.

Group (G) 1 (n=20): Proliferative endometrium
G2 (n=20): EH without atypia
G3 (n=20): EH with atypia
G4 (n=20): Grade-1 endometrioid adenocarcinoma
Blocks from each case were sectioned again and immunohistochemically stained for asprosin.

Immunohistochemistry

Sections with a thickness of 4-6 µm were obtained from paraffin blocks and mounted on polylysine-coated slides. For antigen retrieval, the deparaffinized sections were heated in a citrate buffer solution (pH 6) using a microwave oven (750 W) for 7+5 minutes, following passage through a graded alcohol series. After boiling, the tissues were allowed to cool to room temperature for approximately 20 minutes. Endogenous peroxidase activity was inhibited by washing the tissues with [phosphate buffered saline (PBS), P4417, Sigma-Aldrich, USA] three times for 5 minutes each, followed by incubation in a hydrogen peroxide block solution (Hydrogen Peroxide Block, TA-125-HP, Lab Vision Corporation, USA) for an additional 5 minutes. To minimize background staining, the slides were again washed with PBS (3x5 minutes) and then treated with Ultra V Block solution (TA-125-UB, Lab Vision Corporation, USA) for 5 minutes.

The tissues were subsequently incubated with the primary antibody against asprosin (anti-asprosin antibody, FNab09797, Fine Test, China) diluted 1:200 for 60 minutes at room temperature in a humidified chamber. Following three washes with PBS (5 minutes each), sections were incubated with a secondary antibody (biotinylated Goat Anti-Polyvalent, TP-125-BN, Lab Vision Corporation, USA) for 30 minutes under the same conditions. After another series of PBS washings (3x5 minutes), Streptavidin Peroxidase (TS-125-HR, Lab Vision Corporation, USA) was applied for 30 minutes at room temperature in a humid environment, followed by PBS washings.

For chromogenic visualization, a mixture of AEC Substrate and AEC Chromogen was added until adequate signal development was observed under a light microscope (AEC Substrate, TA-015-HAS, and AEC Chromogen, TA-002-HAC, Lab Vision Corporation, USA). The slides were then rinsed with PBS and distilled water, counterstained with Mayer's hematoxylin, and mounted with the appropriate mounting medium (Large Volume Vision Mount, TA-125-UG, Lab Vision Corporation, USA). Microscopic evaluation and photography were performed using a Leica DM500 microscope equipped with a Leica DFC295 camera.

Immunostaining was semi-quantitatively scored using a histoscore calculated as the product of staining diffuseness and intensity. Diffuseness was graded as 0.1 (<25%), 0.4 (26-50%), 0.6 (51-75%), and 0.9 (76-100%), while staining intensity was rated as 0 (none), +0.5 (very low), +1 (low), +2 (moderate), and +3 (strong). The histoscore was then calculated as (Histoscore = diffuseness x intensity)[18].

Statistical Analysis

Data were presented as mean ± standard deviation. SPSS version 22 was used for statistical analysis. Differences between the groups were analyzed with one-way ANOVA and post-hoc Tukey test. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of immunoreactivity histoscore values to differentiate between proliferative endometrium and grade I endometrial adenocarcinoma. ROC curve analysis results were presented as % specificity and % sensitivity, with area under the ROC curve (AUC), p-value, and 95% confidence interval (CI). P<0.05 was considered statistically significant in all analyses.

Results

As a result of the evaluation of immunohistochemical staining for asprosin immunoreactivity with light microscopy, the immune reactivity of asprosin was determined as cytoplasmic reactivity. Evaluation of immunohistochemical staining for asprosin immunoreactivity under a light microscope revealed no significant difference in asprosin immunoreactivity between the proliferative endometrium group (Figure 1a) and EH without atypia (Figure 1b, p=0.662); and EH with atypia (Figure 1c, p=0.997).

Asprosin immunoreactivity was significantly increased in Grade I endometrial adenocarcinoma when compared with the proliferative endometrium group (Figure 1d, p<0.001) (Table 1).

In the ROC analysis performed to determine the histoscore values of asprosin immuneactivity for the differentiation of proliferative endometrium and grade I endometrial adenocarcinoma. A cut-off value of >0.6 was found to have 100% specificity and 80% sensitivity (AUC=0.968, p<0.001, 95% CI= 0.857-0.998).

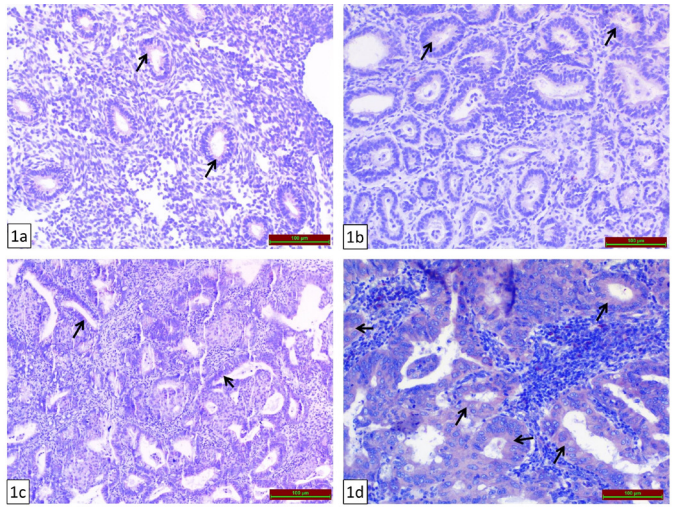

Figure 1. Asprosin immunoreactivity in proliferative endometrium (1a), simple endometrial hyperplasia without atypia (1b), simple endometrial hyperplasia with atypia (1c), complex endometrial hyperplasia without atypia (1d), complex endometrial hyperplasia with atypia (1e), Grade I endometrial adenocarcinoma (black arrow)

Table 1. Asprosin immunoreactivity scores of all groups

Groups	Asprosin immunoreactivity histoscore	p-values
Proliferative endometrium	0.40±0.11	
Endometrial hyperplasia without atypia	0.31±0.12	0.662
Endometrial hyperplasia with atypia	0.36±0.16	0.997
Grade I endometrial adenocarcinoma	0.93±0.35[a]	<0.001

Values are given as mean ± standard deviation.
[a]: Compared with the proliferative endometrium group (p<0.05)

Discussion

The findings of the current study demonstrated that endometrial adenocarcinomas have higher asprosin immunoreactivity than EH and proliferative endometrium without atypia.

During research on neonatal progeroid syndrome, a rare hereditary condition, in 2016, Romere et al.[15]. discovered the protein asprosin to be an adipokine. An increasing number of research since its discovery, indicates that asprosin is useful in controlling metabolic homeostasis and other physiological functions[19]. For instance, it has been demonstrated that asprosin influences hepatic gluconeogenesis and appetite regulation at the hypothalamus level. In addition, there is increasing evidence linking asprosin to intrauterine growth restriction, metabolic diseases, and pregnancy problems, including preeclampsia and gestational diabetes mellitus[20-23]. Studies have shown that long-term high calorie intake causes hypoxia as a result of adipose tissue malfunction leading to oxidative stress and apoptotic pathways[24]. According to Lee et al.[16], asprosin can cause x cells to undergo apoptosis by binding to Toll-like receptor 4 (TLR4) and activating the TLR4/c-JNK-mediated pathway, which raises the levels of proinflammatory cytokines and free oxygen radicals. High levels of oxidative stress and systemic inflammatory pathways are recognized as important in the development of EC as estrogen metabolism[25]. Furthermore, women with polycystic ovary syndrome, which is a significant risk factor for EC along with obesity and diabetes, have been found to have higher levels of circulating asprosin[26]. Studies on the role of asprosin in cancer are limited in the literature. In fact, asprosin therapy of ovarian cancer cells ***in vitro*** has been demonstrated to change cell communication, transforming growth factor -β signaling, and cell proliferation pathways[27]. It has also been demonstrated more recently that circulating asprosin levels can differentiate between serous benign, serous borderline, and malignant ovarian tumors and may serve as a biomarker in ovarian cancer[28]. In the same vein, there was a notable rise in asprosin immunoreactivity in colorectal adenocarcinoma (i.e., grade 1 versus grade 2), and the clinical value of serum asprosin levels was observed in early pancreatic cancer[29,30]. We demonstrated in our study that asprosin immunoreactivity could be helpful in identifying EC in its early stages. We propose that it could be an especially helpful immunohistochemistry marker for identifying whether EH will eventually progress into cancer.

Protein tyrosine phosphatase receptor type D (PTPRD) is known to regulate several key biological functions, including cell proliferation, differentiation, and neoplastic transformation[31]. A recent genome-wide association study (GWAS) meta-analysis identified a locus within the ***PTPRD*** gene associated with endometrial cancer. Moreover, emerging evidence indicates that both asprosin and PTPRD may contribute to the regulation of cancer cell growth and metastasis.

Consequently, it manifests as a gynecological malignancy, the fourth most prevalent disease and the third leading cause of cancer-related deaths among women globally[32,33]. Using clinical and pathology samples from both EH and EC cases, we examined asprosin immunoreactivity in these conditions.

Studies have shown that both EC and glioblastoma multiforme (GBM) exhibit significantly reduced PTPRD expression at the gene and protein levels compared with healthy control tissues. According to reports, signaling pathways implicated in cell proliferation may be compromised by this downregulation[34]. For instance, it has been demonstrated that downregulating PTPRD promotes cell proliferation in the RCAS PDGFB/Nestin-tvA glioma mouse model, where the *p16Ink4a* gene is knocked out; whereas restoring PTPRD expression in GBM cells suppresses cell growth and induces apoptosis[35,36]. It has been demonstrated that loss of PTPRD in gastric malignancies causes an increase in CXCL8, stimulating angiogenic and metastatic events through the STAT3 and ERK signaling pathways[37]. Additionally, PTPRD has been implicated in colon cancer cell migration through the β-catenin/TCF/CD44 signaling pathway, and it has been found to function as a tumor suppressor gene in lung cancer[38,39]. In contrast to proliferative endometrium and EH with and without atypia, we demonstrated in our study that asprosin immunoreactivity increased significantly in endometrial cancer. The elevated asprosin immunoreactivity could be attributable to the previously described pathways. This implies that asprosin might be a useful immunohistochemistry marker for identifying risk factors for EC progression. In the same vein, PTPRD functions via the STAT3 pathway, which is triggered in endometrial cancer[40]. In particular, 11.14% of endometrial samples seem to have a mutation in PTPRD[41]. The *PTPRD* gene is associated with one of the 13 loci linked to EC and endometriosis that were found in a GWAS meta-analysis[32]. Even though PTPRD expression was unaffected by the grade or stage of endometrial cancer, it was demonstrated, that obese EC patients had considerably lower levels of PTPRD than healthy weight controls[34]. Notably, it has been demonstrated that the risk of EC increases by 2.0% for those with a body mass index (BMI) of 25-29.9 kg/m^2, 5.2% for those with a BMI of 30 kg/m^2, and 6.9% for those with a BMI of 40 kg/m^2 or

higher[26]. Collectively, these findings suggest that PTPRD plays a key role in EC as well as a potential tumor suppressor gene. PTPRD expression levels in GBM patients may not be clinically useful as a prognostic biomarker. Nonetheless, obesity has been shown to have no effect on PTPRD expression status in these individuals[34].

The effectiveness of some immunohistochemical markers in predicting the probability of transition from EH to EC has been investigated in the literature[42]. Progesterone receptor-B expression[43], COX-2 expression[44], p53 expression[45], lamin receptor-1 expression[46], TRPM2 and TRPM7[18], and hyaluronan synthase 2[47]. immunoreactivities. According to our research, the asprosin immunoreactivity score was similar to cases of proliferative endometrium but far lower than that of endometrial cancer, even in cases of atypical endometrial hyperplasia. This indicates that asprosin might be a useful immunohistochemistry marker worth investigating in the progression from hyperplasia to malignancy.

Metformin has been reported to decrease circulating asprosin concentrations in patients with diabetes mellitus. Gozel and Kilinc[48] demonstrated that plasma and salivary asprosin levels were significantly reduced in newly diagnosed type 2 diabetes mellitus patients receiving metformin therapy. Similarly, Dashtkar et al.[49] observed that metformin treatment alleviated insulin resistance by lowering asprosin levels in both diabetic and control rats. In addition, their study suggested that metformin modulates asprosin and FBN1 expression, indicating possible mechanisms of action extending beyond its effects on insulin sensitivity.

However, asprosin is being investigated as potentially having important roles in receptor dynamics and signaling pathways in EC. It is emphasized that these studies may provide more detailed information about the biological mechanisms by which asprosin influences endothelial cells EC and identify future therapeutic targets. It is reported that asprosin increases cell proliferation and migration through TLR4 or PTPRD signaling, and inhibiting these receptors may offer a new strategy to limit EC progression[50]. However, metformin has been shown to reduce mortality and prolong survival in patients with type 2 diabetes mellitus and EC[51].

Considering the results of existing studies, the use of asprosin inhibitors in addition to progesterone and metformin may be an effective treatment strategy for both reducing the potential for EH to progress to cancer and treating early-stage EC. Further studies on this topic are warranted.

Study Limitations

Limitations of our study include the limited number of cases due to its retrospective nature, the amount of asprosin in tissue and blood could not be measured biochemically. Furthermore, the inability to measure asprosin gene expression is another limitation of our study. Unlike the above studies, the strength of our study is that it asprosin immunoreactivity was compared in cases of proliferative endometrium, EH with and without atypia, and endometrial cancer.

Conclusion

The significant increase in asprosin immunoreactivity in grade I endometrioid adenocarcinoma, compared to EH (with and without atypia), normal proliferative endometrium suggests that molecules related to energy metabolism, in addition to atypia, may play an important role in the transition from hyperplasia to endometrial cancer.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Fırat University Non-Interventional Research Ethics Board (date: 13.01.2022, number: 2022/01-07).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ş., Ş.Y., R.A., N.Y., Ş.P., B.Ç., Concept: Ş.Y., R.A., T.K., Design: A.Ş., Ş.Y., R.A., Data Collection or Processing: H.B., S.H., T.K., Ş.P., B.Ç., Analysis or Interpretation: A.Ş., Ş.Y., R.A., T.K., Literature Search: A.Ş., Ş.Y., R.A., N.Y., H.B., S.H., Ş.P., M.Y. Writing: Ş.Y., R.A.

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