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# IMMUNOHISTOCHEMICAL EVALUATION, MOLECULAR INVESTIGATION AND DIFFERENTIAL DIAGNOSIS OF A NOVEL ADIPOCYTOKINE CHEMERİN IN OVARIAN AND UTERINE CANCERS

# YENİ BİR ADİPOSİTOKİN OLAN KİMERİNİN OVER VE UTERUS KANSERLERİNDE İMMÜNOHİSTOKİMYASAL DEĞERLENDİRMESİ, MOLEKÜLER ARAŞTIRMASI VE AYIRICI TANISI

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**Abstract**
Patients diagnosed with the following histological types of carcinoma were included in the study: ovarian serous carcinoma (n=16), ovarian endometrioid carcinoma (n=12), ovarian mucinous carcinoma (n=11), uterine serous carcinoma (n=12) and uterine endometrioid carcinoma (n=15). The study was conducted between 2014 and 2023. The study is based on the comparison of two groups of patients with differing levels of organ involvement. Following the extraction of serum from blood samples, the samples were stored in a temperature of -20°C. The measurement of serum chemerin levels was conducted by means of the ELISA method. In the immunohistochemical study, the sections obtained from the tissues in paraffin blocks were stained for chimerine with the Leica Bond max closed system automatic staining device and Bond polymer refine detection (DS9800, Buffalo Grove, United States) DAB compatible kit. In the immunohistochemical study, the presence or absence of chimerin expression in tumour cells was examined. In the group where such expression was observed, the percentage of staining in the cells was calculated. Furthermore, clinical, laboratory and radiological findings were obtained from the hospital system.

**Keywords:** Adipocyte, Chemerin, Gynecological Carcinoma, Ovarian Carcinoma, Uterine Carcinoma.

**Öz**
2014-2023 yılları arasında over seröz karsinom (n:16), over endometrioid karsinom (n:12), over müsinöz karsinom (n:11), uterus seröz karsinom (n:12) ve uterus endometrioid karsinom (n:15) tanılı olgular çalışmaya alınmıştır. Çalışma iki farklı organ tutulumu olan hasta gruplarının birbiriyle karşılaşılması üzerine kuruludur. Kanlardan serum elde edildikten sonra -20°C'de serumlar saklanıp, serum chemerin düzeyleri ELISA yöntemi ile ölçülmüştür. İmmünohistokimyasal çalışmada, parafin bloklardaki dokulardan elde edilen kesitlerde Leica bond max kapalı sistem otomatik boyama cihazı ile Bond polymer refine detection (DS9800, Buffalo Grove, United States) DAB uyumlu kit eşliğinde chemerin çalışılmıştır. İmmünohistokimyasal çalışmada tümör hücrelerinde chemerin ekspresyonunun varlığı/yokluğu incelenmiştir. Ekspresyon izlenen grupta hücrelerin yüzde kaçında boyanma olduğu hesaplanmıştır. Hastane sisteminden hastalara ait klinik, laboratuvar ve radyolojik bulguları da verifiye edilmiştir.

**Anahtar Kelimeler:** Adiposit, Kemerin, Jinekolojik Karsinom, Over Karsinomu, Uterin Karsinomu.

## 1. Introduction

Uterine cancer is the most prevalent malignancy in the field of gynaecology, with a high mortality rate. Current global estimates place uterine cancer as the fourth most prevalent cancer among the female population worldwide (Teng et al., 2023). A correct diagnosis is paramount for the prognosis and appropriate treatment of patients with this condition. Early diagnosis can facilitate timely treatment decisions and reduce the economic burden of treatment. Ovarian cancer, the third most prevalent cancer within the female reproductive system, is characterised by the highest mortality rate. Ovarian cancer is characterised by its biological behaviour and the absence of specific early symptoms, which often results in diagnosis at an advanced stage of the disease. Approximately 60-70% of cases are diagnosed at FIGO III and IV stages (Maringe et al., 2012). This late diagnosis inevitably results in a poorer prognosis for patients. While the five-year survival rate for patients with stage I and II disease is 80-90%, this rate drops to 30-50% for stage III and IV patients. Despite advances in our understanding of the biology of this cancer, there is still a lack of markers with high specificity and sensitivity for ovarian cancer that have entered medical practice. While the most widely used biomarker of ovarian cancer is plasma CA-125 levels, this is not applicable as a screening test (87% specificity, 70% sensitivity) (Stewart et al., 2019). The identification of novel biomarkers for the diagnosis and prevention of ovarian cancer is, therefore, a significant area of research (Menon et al., 2021).

White adipose tissue is an active organ that secretes a variety of proteins, known as adipocytokines, which play a role in the regulation of metabolism, immunity, the endocrine system and inflammation (Juge-Aubr et al., 2005). Chemerin, a recently discovered adipokine, has been shown to play a significant role in the process of adipogenesis and the chemotaxis of the innate immune system (Rourke et al., 2013). It has been identified in various tissues, including those found in the adipose tissue, liver, pancreas, and skin, which regulate the function of innate immune cells (Barnea et al., 2008). Chemerin, a recently identified adipokine, has been demonstrated to contribute to adipogenesis and lipid metabolism, cell proliferation, inflammation, and endothelial angiogenesis (Roh et al., 2007). In addition, studies suggest a potential association between chemerin and cancer development. Indeed, studies have shown that chemerin expression is significantly reduced in liver cancer, skin cancer and melanoma compared to normal and/or benign tumours (Pachynski et al., 2012). Conversely, another study found that chemerin expression was elevated in colorectal cancer and gastric cancer (Ahn et al., 2016). These findings suggest that changes in chemerin expression may have a significant effect on tumour formation and progression. However, the role of 'Chemerin' adipocytokinin, categorised as 'new adipocytokines', in ovarian and uterine cancer remains to be fully elucidated. The role of this adipocytokinin in differential diagnosis remains to be elucidated. To the best of the present author's knowledge, no experimental study on this subject has been published in the literature.

The characterisation of the molecular mechanisms involved in cancer progression may facilitate the identification of prognostic markers and new therapeutic targets. The present study aims to contribute to the existing literature by identifying novel adipocytokines involved in ovarian and uterine cancer, by identifying markers that can be used in the diagnosis of ovarian and uterine cancer, and by developing targeted therapy and analysing its usefulness in differential diagnosis.

## 2. Material and Methods

### *2.1. Creation of patient and control groups and obtaining serum*

Serum samples were collected from patients diagnosed with the following histological subtypes of ovarian carcinoma: serous carcinoma (n = 16), endometrioid carcinoma (n = 12), mucinous carcinoma (n = 11), uterine serous carcinoma (n = 12) and uterine endometrioid carcinoma (n = 15). These samples were collected from the Department of Pathology at Amasya University between 2014 and 2023. Serum samples from a control group (n = 20) were also collected for comparison. Serum samples were then stored at -20°C until ELISA experiments were performed.

### *2.2. Measurement of chemerin levels in serum by ELISA*

The measurement of serum chemerin levels was conducted in accordance with the quantitative sandwich enzyme immunoassay technique, employing an ELISA kit (Elabscience, Houston, Texas, United States of America, Catalogue Number

E-EL-H0698). This commercial kit has a sensitivity of 0.10 ng/mL and both inter- and intra-assay coefficients of variation were <10%. It is imperative to note that all standards and samples were run in duplicate. A volume of 100 µl of each standard and sample was added to the wells. The plate is then covered with gelatin using adhesive tape and incubated at 37°C for 90 minutes. The next step involves the removal of the contents from the wells and the addition of 100 µl of biotinylated chemeric antibody at a concentration of 1X. The microplate is then left to incubate at 37°C for a period of 60 minutes. The wells are then emptied and washed on three occasions. Finally, 100 µl of HRP conjugate at 1X concentration is added to each well and the plate is left to incubate at 37°C for 30 minutes. The wells are then washed on five separate occasions. Subsequently, 90 µl of substrate solution is added to the wells, after which the plate is covered and incubated at 37°C for 15 minutes. Immediately after the addition of 50 µl of reaction stop solution to each well, the absorbances of the wells are measured at 450 nm. The concentration and light absorption of the standards are then utilised to calculate the level of chimerine in the serum, employing the standard curve.

*2.3. The presence of immunohistochemical staining of chemerin*

An immunohistochemical study was conducted in the pathology department of our hospital on paraffin-blocked tissues from patients with newly diagnosed cases. The aim of the study was to examine the presence/absence of expression of tumour cells with immunohistochemical markers.

*2.4 Statistical analysis*

The data are presented as the mean ± standard error of the mean, and the mean values between the two groups are compared by Student's t test. Pearson's correlation test is utilised to ascertain the relationship between serum and gene expression levels of adipocytokines and other variables. It is imperative to note that all reported confidence interval values are calculated at the 95 per cent level. A P value less than 0.05 is considered to indicate a statistically significant result.

## 3. Results and Discussion

The results of the study revealed that a total of 39 ovarian cancer groups were diagnosed with ovarian serous carcinoma (OSC) (n:16), ovarian endometrioid carcinoma (OEC) (n:12), and ovarian mucinous carcinoma (OMC) (n:11). In addition, 27 uterine cancer groups were diagnosed with uterine serous carcinoma (USC) (n:12), uterine endometrioid carcinoma (UEC) (n: 15) diagnosed with a total of 27 uterine cancers compared with the control group (CG) (n=20), it was found that serum chemerin levels did not show a statistically significant change in both ovarian and uterine cancer groups compared to the control group (Table1-3).

The ovarian cancer group exhibited a p-value of 0.52 when compared to the control group, and the uterine cancer group demonstrated a p-value of 0.35 when contrasted with the control group.

**Table 1.** Pathological data of carcinomas

| Parameters | OSC | OEC | OMC | USC | UEC |
|---|---|---|---|---|---|
| **Tumor size** | (n) | (n) | (n) | (n) | (n) |
| **T1** | 12 | 11 | 11 | 10 | 12 |
| **T2** | 4 | 1 | 0 | 2 | 3 |
| **T3** | 0 | 0 | 0 | 0 | 0 |
| **Nodal statü** | (n) | (n) | (n) | (n) | (n) |
| **N0** | 12 | 10 | 10 | 4 | 6 |
| **N1** | 4 | 2 | 2 | 4 | 4 |
| **N2** | 0 | 0 | 0 | 4 | 5 |
| **FİGO stage** | (n) | (n) | (n) | (n) | (n) |
| **I** | 12 | 11 | 11 | 10 | 12 |
| **II** | 4 | 1 | 0 | 2 | 3 |
| **III** | 0 | 0 | 0 | 0 | 0 |

**Table 2.** Immunohistochemical data

| **Estrogen receptor** | **(n)** | **(n)** | **(n)** | **(n)** | **(n)** |
|---|---|---|---|---|---|
| **Negative** | **11** | **4** | **6** | **4** | **0** |
| **Positive** | **5** | **8** | **5** | **8** | **15** |
| **P53** | (n) | (n) | (n) | (n) | (n) |
| **Mutant** | 16 | 1 | 0 | 12 | 0 |
| **Not mutant** | 0 | 11 | 11 | 0 | 15 |
| **WT1** | (n) | (n) | (n) | (n) | (n) |
| **Negative** | 1 | 11 | 11 | 3 | 10 |
| **Positive** | 15 | 1 | 0 | 9 | 5 |
| **Chemerin** | (n) | (n) | (n) | (n) | (n) |
| **Negative** | 14 | 11 | 11 | 12 | 14 |
| **Positive** | 2 | 1 | 0 | 0 | 1 |

**Table 3.** Serum data and blood pressure data

| | | | | | |
|---|---|---|---|---|---|
| **Serum chemerin (ng/ml)** | 371.05±84.35 | 363.27±77.49 | 373.24±61.49 | 348.27±57.46 | 375.82±64.44 |
| **Total cholesterol (mg/dl)** | 168.18±41.60 | 153.2± 40.64 | 128.18±21.60 | 168.26±41.25 | 148.36±45.25 |
| **Triglycerides (mg/dl)** | 146.28±52.31 | 136.22±45,26 | 166.36±56.21 | 156.28±52.26 | 146.28±54,32 |
| **HDL cholesterol (mg/dl)** | 37.68 ± 12.66 | 36.67± 10.61 | 40.68± 13.60 | 38.95± 11.26 | 36.69± 13.46 |
| **LDL cholesterol (mg/dl)** | 101.12±35.33 | 101.25±35.30 | 100.24±31.30 | 104.12±34.23 | 103.03±36.12 |
| **Systolic blood pressure (mmHg)** | 129.88±12.22 | 129.88±12.22 | 129.88±12.22 | 129.88±12.22 | 129.88±12.22 |
| **Diastolic blood pressure (mmHg)** | 81.63± 11.00 | 80.62± 10.00 | 82.63± 10.23 | 81.98± 12.00 | 80.63± 10.10 |

Among gynaecological malignancies, ovarian cancers have the highest mortality rate. Ovarian serous carcinoma accounts for 46% of surface epithelial tumours of the ovary. Mucinous carcinomas, on the other hand, are observed less frequently. Despite the observed variations in ovarian cancer incidence across different geographical regions, the mortality rate stands at 9%, with a five-year survival rate of approximately 41.0% (Nucci et al., 2009). The majority of endometrial carcinomas are of the endometrioid type, while mucinous and endometrial serous carcinomas are less common (Tavassoli et al., 2003). However, endometrial serous carcinomas are responsible for approximately 40% of endometrial cancer-related deaths (Moore et al., 2011). Despite the utilisation of analogous chemotherapeutic agents in tumours originating from both organs, treatment algorithms diverge (Zhang et al., 2020). Furthermore, the differing staging of primary ovarian and primary endometrial tumours underscores the necessity for a differential diagnosis of these tumours (Tavassoli et al., 2003). White adipose tissue is an active organ that secretes a variety of proteins, known as adipocytokines, which play a role in the regulation of metabolism, immunity, the endocrine system and inflammation. Chemerin, a recently discovered adipokine, has been shown to play a significant role in the process of adipogenesis and the chemotaxis of the innate immune system. The role of 'Chemerin' adipocytokinin, which is currently termed 'new adipocytokines', in ovarian and uterine cancers is not yet fully understood. The potential of this adipocytokine in the context of differential diagnosis remains to be elucidated. To the best of the authors' knowledge, there have been no experimental studies on this subject in the literature. The present study aims to determine the role of this adipocytokinin in the etiology of ovarian and uterine cancers, to analyse its usability in differential diagnosis and to contribute to the existing literature on the subject.

In the present study, no significant difference was observed between the groups with regard to serum chemerin levels. It is well established that there is a close relationship between metabolism and reproductive function (Schneider et al., 2005). Adipose tissue is recognised as an endocrine organ that can influence fertility through the secretion of adipokines, which are cytokines involved in various physiological processes (Scheja et al., 2019). These biologically active proteins are recognised as the principal regulators of whole body energy homeostasis (Luo et al., 2016). A substantial body of research has already identified and discussed the important roles of leptin and adiponectin in different physiological processes, including reproduction (Barbe et al., 2019). In this study, the focus has been directed towards the effect of Chemerin adipocytokinin on reproductive system cancers, which have been identified and recognised as significant regulators of energy metabolism. Chemerin and its primary receptor CMKLR1 are expressed in white adipose tissue, and elevated circulating levels of this adipokine have been observed in obesity and metabolic syndrome (Bozaoglu et al., 2007). Chemerin is a proinflammatory cytokine that recruits and activates immune cells and contributes to inflammation by promoting macrophage adhesion to vascular cell adhesion molecule-1 (VCAM-1) and fibronectin, suggesting that it may also play a role in the relationship between obesity and inflammation (Ouchi et al., 2011). In humans, chemerin has been predominantly detected in white adipose tissues, liver and placenta, and to a lesser extent in brown adipose tissue, lungs, skeletal muscles, kidneys, ovaries and heart. Chemerin is a cytokine that plays a regulatory role in various physiological processes, including immune system regulation, angiogenesis and inflammation (Mattern et al., 2014). In the present study, no significant difference was observed between systolic and diastolic blood pressures, HDL, LDL, total cholesterol levels and chemerin. The relationship between chemerin and cancer remains to be fully elucidated. However, it has been demonstrated that chemerin can promote angiogenesis by inducing matrix metalloproteinase secretion and activity. Consequently, it is hypothesised that elevated levels of chemerin may contribute to the initiation of carcinogenesis and subsequent metastasis. In contrast, chemerin has been demonstrated to recruit natural killer cells, which have been hypothesised to function as a primary component in cell defence, exhibiting tumour suppressor properties (Skrzeczynska-Moncznik et al., 2009). Chemerin expression has been observed in mouse ovaries under normal physiological conditions (Goralski et al., 2007). Furthermore, Chemerin has been detected in non-tumour human myometrial cells and fibrotic cells by means of microarray and real-time quantitative polymerase chain reaction (RT-qPCR) (Zaitseva et al., 2008). Chemerin expression has been monitored in human primary cell cultures obtained from stromal and extravillous trophoblastic cells from pregnant women. It has been hypothesised that Chemerin levels increase during decidualisation, potentially contributing to natural killer (NK) cell accumulation and vascular remodelling during the early stages of pregnancy (Carlino et al., 2012). Chemerin, a chemotactic agent, has been detected in the rat placenta during pregnancy and is also expressed in human placenta. The role of Chemerin in placentation is characterised by its ability to regulate NK cell accumulation and endothelial cell morphogenesis during the early stages of pregnancy. In the context of pre-eclampsia, Chemerin has been found to play a protective role by regulating umbilical cord vessel endothelial cell-derived nitric oxide signalling, and is expressed in the umbilical cord (Wang et al., 2015).

## 4. Conclusion

The objective of the study was to utilise the parameter as a diagnostic tool to alert clinicians to the potential emergence of new lesions during the initial diagnosis and subsequent follow-up of patients diagnosed with ovarian and uterine cancer. Consequently, it would serve as an alternative to the costly and challenging to access imaging methods employed for follow-up. From this standpoint, the objective was to prevent patients from seeking care at third-step hospitals, as it was a non-invasive procedure that could be readily available in smaller medical facilities. Furthermore, given its non-invasive nature, it is anticipated that this procedure would provide a less traumatic experience for patients, enhancing their comfort levels. However, given that no significant difference was observed between the groups, the chemerin cannot serve this purpose at this time.

With regard to pathological contributions, the determination of tissue markers would facilitate the work of pathologists in differential diagnosis of patients and guide them during primary focus analyses of metastatic masses. However, given that no significant differences were observed between the groups, the chemistry cannot fulfil this role at present. It is hypothesised that the limited number of patients is a contributing factor to the absence of a significant difference between the groups. It is

recommended that the study be repeated with a larger patient cohort to ascertain the significance of the findings.

**The ethical dimension of the research**

Approval was obtained from the amasya university non-interventional clinical research ethics committee on 03.02.2022 with decision no: 19.

**Conflicts of interest:** No conflict of interest

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