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Research Article

The importance of adropin and hypoxia inducible factor-1 alpha in gastric cancer

Mide kanserinde adropin ve hipoksi ile indüklenebilir faktör -1 alfa'nın önemi

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Abstract

Aim: Gastric cancer accounts for 5.6% of all new cancer cases worldwide and is the fifth most common type of cancer. It ranks third in cancer-related mortality. With the current standard neoadjuvant treatment of localised gastric cancer, appropriate resection can be performed in approximately 75% of patients. While the two-year survival rate of patients is approximately 70 %, this rate decreases to 45 % in the fifth year. Although high curative treatment rates and long-term survival success are achieved with early diagnosis in many cancer types, unfortunately the same is not the case for gastric cancer and the unmet need for treatment continues. Adropin is a peptide secreted from many tissues in our body and has a regulatory role in energy homeostasis, angiogenesis, cell proliferation and cell migration processes. Hypoxia-inducible factor (HIF) is activated when oxygen levels decrease in tissues and regulates the growth, development, and differentiation of cells. A prospective study was planned to investigate the role of adropin and HIF-1α on the pathogenesis of gastric cancer and the relation of treatment response rates with adropin and HIF-1α levels by comparing adropin and HIF-1α levels in newly diagnosed locally advanced gastric cancer patients with adropin and HIF-1α levels in healthy individuals.

Material and Methods: Adropin and HIF-1α levels were compared between newly diagnosed patients with localised gastric cancer receiving neoadjuvant chemotherapy and healthy control group. We also examined whether there was a correlation between clinical and pathological response rates and adropin and HIF-1α levels in patients who completed the treatment.

Results: Adropin levels were statistically significantly lower and HIF-1α levels were statistically significantly higher in patients with gastric cancer. No significant difference was observed between adropin and HIF-1α levels and various clinical variables such as clinical response, pathological response, operability status, new pathological T (ypT) and new pathological N (ypN) stages..

Conclusion: It was important to demonstrate the relationship between adropin and gastric cancer, which had not been previously investigated and for which no data were identified through a literature review. It is obvious that adropin and HIF-1α are two important factors involved in gastric cancer. In addition adropin and HIF-1α may be two important parameters for early diagnosis of gastric cancer. Further studies are needed to elucidate the role of adropin and HIF-1α in gastric cancer.

Keywords: adropin, HIF-1α, gastric cancer

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Öz

Amaç: Mide kanseri tüm dünyada ki yeni kanser vakalarının %5,6'sını oluşturur ve beşinci en sık görülen kanser türüdür. Kansere bağlı ölüm sıralamasında ise üçüncü sırada yer almaktadır. Lokalileri mide kanserinde, günümüzde ki standart neoadjuvan tedavi ile hastaların yalaşık % 75'ine uygun rezeksiyon yapılabilmektedir. Hastaların iki yıllık hayatta kalma oranları yaklaşık %70 iken bu oran beşinci yılda %45'lere düşmektedir. Bir çok kanser türünde erken tanı ile yüksek küratif tedavi oranları ve uzun süreli sağkalım başarısı sağlanmasına rağmen mide kanseri için malesef aynı durum sözkonusu değildir ve karşılanmamış tedavi ihtiyacı devam etmektedir. Adropin, vücudumuzda birçok dokudan salgılanan; başlıca enerji homeostazisi, anjiyogenez, hücre proliferasyonu ve hücre göçü süreçlerinde düzenleyici rolü olan bir peptittir. Hipoksi ile indükenebilir faktör (HIF) ise dokularda oksijen seviyeleri düşünce aktive olur ve hücrelerin büyümesi, gelişmesi ve farklılaşmasını regüle eder. Yeni tanı almış lokal ileri mide kanseri hastalarında ki adropin ve HIF-1α sevyeleri ile sağlıklı bireylerdeki adropin ve HIF1-α seviyeleri karşılaştırılarak, adropinin ve HIF1-α'nın mide kanseri patogenezi üzerinde rolü ve tedavi yanıt oranlarının adropin ve HIF-1α seviyeleri ile ilişkisinin araştırılması amacıyla prosektif bir çalışma planlandı.

Gereç ve Yöntemler: Yeni tanı almış, neoadjuvan kemoterapi alacak olan lokalileri mide kanserli hastalar ve sağlıklı kontrol grubu arasında adropin ve HIF-1α düzeyleri karşılaştırıldı. Ayrıca tedaviyi tamamlayan hastalarda klinik ve patolojik yanıt oranları ile adropin ve HIF-1α düzeyleri arasında bir ilişki olup olmadığına bakıldı.

Bulgular: Adropin, mide kanserli hastalarda istatistiksel anlamlı olarak daha düşük, HIF-1α düzeyleri ise mide kanserli hastalarda istatistiksel anlamlı olarak daha yüksek bulundu. Adropin ve HIF-1α düzeyleri ile klinik yanıt, patolojik yanıt, operabilite durumu, yeni patolojik T (ypT) ve yeni patolojik N (ypN) evreleri gibi çeşitli klinik değişkenler arasında anlamlı bir farklılık görülmedi.

Sonuç: Daha önce araştırılmamış olan ve literatür taraması yoluyla herhangi bir veri tespit edilemeyen adropin ve mide kanseri arasındaki ilişkiyi ortaya koymak önemliydi. Adropin ve HIF-1α'nın mide kanserinde rol oynayan iki önemli faktör olduğu açıktır. Ayrıca adropin ve HIF-1α mide kanserinin erken teşhisi için iki önemli parametre olabilir. Adropin ve HIF-1α'nın mide kanserindeki rolünü aydınlatmak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: adropin, hıf-1α, mide kanseri

Introduction

Gastric cancer accounts for 5.6% of all new cancer cases worldwide and is the fifth most common type of cancer. It ranks third in cancer-related mortality (1). Gastric cancer varies in terms of gender and geographical distribution. It is particularly common in East Asia, Central-South America and Eastern Europe and is about twice as common in males as in females (1). In addition to advanced age, risk factors include genetic predisposition, diet, alcohol, smoking, and helicobacter pylori infection (2). Since there is no effective screening method for the early diagnosis of gastric cancer, more than two-thirds of patients are diagnosed at an advanced stage (3). A small proportion of patients are diagnosed at the local-local advanced disease stage. Local disease is defined as a tumour limited to the mucosa and submucosa and is treated by surgical resection. Locally advanced disease is defined as tumours between T2-T4a according to TNM staging system or tumours with lymph node infiltration (N+) (4). Locally advanced tumours are resectable tumours, but disease recurrence occurs in the majority of patients after surgery and five-year survival is between 10-15% (5). For this reason, the MAGIC study comparing surgery with preoperative epirubicin cisplatin 5-fluorouracil (EPC) chemotherapy was performed and it was shown that the results of preoperative chemotherapy were better (5). In the FLOT4 study, which compared EPC treatment before surgery with 4 cycles of dozataxel, oxaliplatin, 5-fluorouracil (FLOT) treatment before and after surgery, FLOT treatment improved pathological complete response (PCR), disease-free survival (DFS) and overall survival (OS) rates and is now considered the standard treatment (6). However, disease recurrence was observed in patients treated with FLOT before and after surgery and the mean survival was reported to be 50 months. In addition, pathological minimal response or non-response was observed in almost half of the patients after neoadjuvant treatment (6). In the view of this information, it is obvious that there are unknown factors such as histological type, genetic mutations, biochemical parameters that affect the character of the disease, prognosis, and chemotherapy response. Many guiding studies are needed to elucidate these factors.

Adropin is a peptide consisting of 76 amino acids discovered by Kumar et al. in 2008 (7). It is encoded by a gene called energy homeostasis associated gene (Enho) located on chromosome 9 and is expressed in many tissues in the human body (Figure 1). Adropin has been shown to stimulate angiogenesis, proliferation, and migration of endothelial cells via vascular endothelial growth factor receptor-2 (VEGFR2) (8). Adropin has also been suggested to increase endothelial nitric oxide (NO) levels via VEGFR2 and phosphatidylinositol 3-kinase-Akt (PIK3-AKT). NO improves endothelial cell functions, shows protective effect on endothelial cells and regulates angiogenesis (8). These findings suggest that adropin may be related to the regulation of angiogenesis in tumour cells, cell proliferation and migration, and response to treatment. A recent study showed that G-protein coupled receptor 19 (GPR19), an adropin receptor, is highly expressed in colorectal cancer (CRC) tissue. It was shown that adropin may play a role in regulating the energy homestasis of tumour tissue and in inflammatory-proinflammatory regulation by affecting macrophages in the tumour microenvironment. It has been reported that different tumour behaviour was observed at different levels of adropin (9). In a study investigating the correlation between adrenocortical carcinoma and adropin, it was shown that GPR19 was highly expressed in tumour tissue, exogenous adropin administration increased proliferation in tumour cells and was shown to be a poor prognostic factor for disease progression (10). Similarly, studies investigating the correlation of adropin with endometrial cancer (11), pancreatic ductal adenocarcinoma (12), and breast cancer (13) were also conducted and different results were obtained.

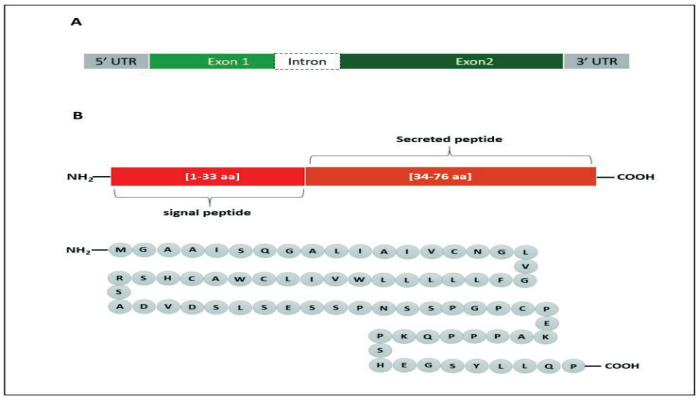

Figure 1: Structure of the Enho Gene and Adropin

Hypoxia-inducible factor (HIF) is a transcriptional factor involved in the regulation of oxygenation, an essential requirement for the growth, development, and differentiation of all living tissues. Ensuring oxygenation is also very important for tumour cells. It has been shown that HIF is activated in the tumour bed and different levels of HIF are associated with different tumour behaviours (14). HIF consists of two subunits, alpha and bata, and the alpha subunit is responsible for the regulation of oxygenisation (15). The alpha subunit is unstable when oxygen levels are high and is rapidly destroyed by pathways involving von Hippel-Lindau tumour suppressor protein (pVHL) (16). When the oxygen level decreases, the alpha subunit stabilises, dimerises with the beta subunit and activates the transcription of a series of genes. In studies conducted on this subject, it has been shown that HIF activation is related with tumour progression, regulation of vascularisation, cell proliferation, invasion and migration; it is also related with treatment resistance (17, 18) (Figure 2). In a recent study, HIF activation was shown to mediate the escape of cancer from the immune system (19). In the view of this information, many studies have been carried out in which some HIF inhibitors can be used in cancer treatment, but they have not been successful due to toxicity.

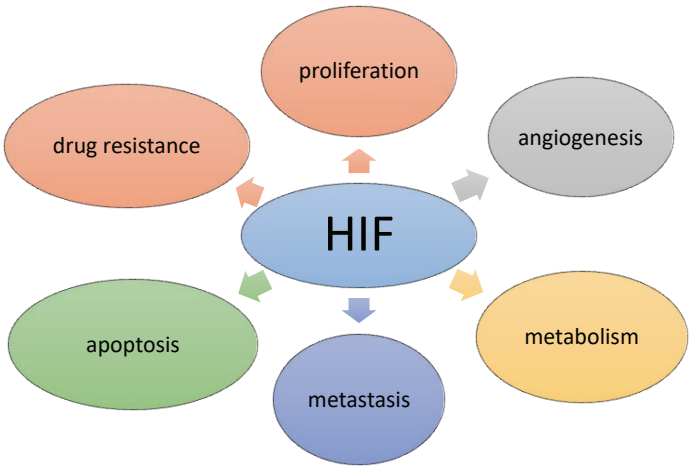

Figure 2: Processes Involved in Hif-1 Alpha in Gastric Cancer

Objective of the Study

There are many unknowns in the pathogenesis of gastric cancer and especially in response to treatment. By comparing adropin and HIF-1α levels in newly diagnosed locally advanced gastric cancer patients with adropin and HIF-1α levels in healthy individuals, we aimed to show whether adropin and HIF-1α have a role in the pathogenesis of gastric cancer and the correlation of clinical and pathological response rates after treatment with adropin and HIF-1α levels.

Material and Methods

A prospective study was planned by including newly diagnosed patients aged 18-80 years with locally advanced gastric cancer who applied to the Medical Oncology Clinic of Atatürk University Faculty of Medicine Hospital since October 2023 on a voluntary basis. Approval was obtained from Atatürk University Faculty of Medicine Clinical Research Ethics Committee. Our study was conducted in accordance with the rules of the World Medical Association (WMA) Declaration of Helsinki. Patients with type 2 diabetes mellitus, body mass index (BMI) <18 and >30, and Eastern Cooperative Oncology Group (ECOG) performance status 2 and above were excluded from the study. Age, gender, height, weight, ECOG performance score and presence or absence of chronic diseases were recorded at the time of initial diagnosis. Blood samples were taken from the volunteer control group (50 people) and patients eligible for the study (50 people) after fasting for 8 hours before treatment and centrifuged and stored at -80 degrees centrifugation. Adropin and HIF-1α were then analysed from the samples of 40 patients who completed the treatment process and whose information could be accessed. Adropin and HIF-1α kits were provided by the researchers. Positron emission tomography (PET-CT) results of the patients after treatment were then evaluated. According to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1), complete response (score 1), partial response (score 2), stable disease (score 3) and progressive disease (score 4) were graded. In the operated patients, the tumour regression score was graded as pathological complete response (score 0), near complete response (score 1), partial response (score 2) and poor response or no response (score 3) according to the College of American Pathologists; 2017 protocol. Adropin and HIF-1α levels in the control and study groups were compared. In the study group, the correlation between adropin and HIF-1α levels and clinical and pathological response rates was examined. All analyses were performed using SPSS (SPSS version 25.0) statistical software package and $p < 0.05$ was accepted as statistical.

Results

SPSS 25.0 package programme was used for data analysis in the study. Descriptive data on the sociodemographic information of the participants are given as frequency tables (N and %). Data on continuous variables are given as median (IQR).

The data of the study were analysed in terms of normality assumptions Kolmogorov-Smirnov values ($p<0.05$). In this respect, Mann Whitney U test and Kruskall Wallis test, which are nonparametric tests, were performed to determine whether there is a significant difference between the groups with various variables. A P value less than 0.05 was considered statistically significant.

The data of forty locally advanced gastric cancer patients who were included in the study and whose information could be recorded completely until the last follow-up date were analysed. Among the patients, 27 (67.5%) were males and 13 (32.5%) were females. Mean age was 61.5 years and mean BMI was 26.1. The mean age and BMI were similar with the control group. After neoadjuvant chemotherapy, PET CT was performed and treatment response evaluation according to RECIST 1.1 criteria showed clinical complete response in 7 (17.5%) patients, partial response in 23 (67.5%) patients, stable disease in 6 (15%) patients and progression in 4 (10%) patients. A total of 25 (62.5%) patients underwent gastrectomy and d2 lymph node dissection, 22 of whom underwent R0 (negative surgical margin) and 3 underwent R1 (positive surgical margin) resection, and 15 (37.5%) patients were found unsuitable for surgery. In the operated patients, tumour regression score was checked according to the College of American Pathologists; 2017 protocol. 6 (25%) patients showed pathological complete or near complete response, 9 (37.5%) patients showed partial response and 9 (37.5%) patients showed non-response or poor response (Table 1).

Table 1. Distribution of various clinical and sociodemographic variables

Variables	Total (n=40)
Age, Mean±SD	61,5±7,2
BMI, Mean±SD	26,1±4,4
Gender, n (%)	
Male	27 (67,5)
Female	13 (32,5)
Clinical response, n (%)	
Complete response	7 (17,5)
Partial response	23 (67,5)
Stable disease	6 (15)
Progressive disease	4 (10
Pathological response, n (%)	
Complete and near complete	6 (25,0)
Partial response	9 (37,5)
No response	9 (37,5)
YpT, n (%)	
T1-T2	7 (29,2)
T3-T4	17 (70,8)
YpN, n (%)	
Lymph node Negative	9 (39,1)
Lymph node Positive	14 (60,9)
Resection, n (%)	
Operated	25 (62,5)
Non-operated	15 (37,5)

ypT: new pathological T stage, ypN: new pathological N stage

In the comparison of adropin and HIF-1α values between patients with gastric cancer and healthy control group, adropin values were found to be statistically significantly lower in patients with gastric cancer (p<0.001). HIF-1α levels were found to be significantly higher in patients with gastric cancer (p<0.001) (Table 2).

Table 2: Comparison of Adropin and HIF-1α Variables with Groups

	Group		
	Patient (n=30) Median (IQR)	Control (n=30) Median (IQR)	p
Adropin (pg/mL)	112,1 (55,1)	295,8 (217,2)	<0.001
HIF-1α (ng/ml)	14,9 (10,2)	1,10 (0,5)	<0.001

Mann Whitney U test, p<0.05 is statistically significant

Furthermore, no significant difference was found between adropin and HIF-1α levels and various clinical variables such as clinical response, pathological response, operability status, ypT and ypN stages (p>0.05) (Table 3).

Table 3: Comparison of Adropin and HIF-1α Variables with Various Clinical Variables

Variables	n	ANDROPIN Median (IQR)	p	HIF1-alpha Median (IQR)	p
Clinical response, n (%)					
Complete response	5	103,4 (75,3)	0.903[b]	19,6 (6,1)	0.721[b]
Partial response	18	122,4 (79,8)		9,8 (12,3)	
Stable disease	6	133,7 (120,1)		12,5 (13,1)	
Pathological response, n (%)					
Complete and near complete	4	127,2 (28,6)	0.699[b]	17,2 (13,6)	0.164[b]
Partial response	8	112,5 (104,2)		9,3 (7,1)	
No response	7	134,5 (104,7)		19,8 (14,2)	
YPT, n (%)					
Early stage	5	122,4 (101,5)	0.926[a]	14,7 (15,0)	0.405[a]
Advanced stage	14	122,2 (63,9)		16,3 (11,2)	
YPN, n (%)					
Negative	7	113,6 (35,1)	0.800[a]	14,6 (13,3)	0.837[a]
Positive	12	127,2 (91,2)		15,2 (11,1)	
Resection, n (%)					
Operated	19	122,4 (50,3)	0.102[a]	14,7 (11,7)	0.355[a]
Non-operated	11	98,8 (35,1)		15,1 (8,9)	

a: Mann Whitney U test, b: Kruskall Wallis test, p<0.05 is statistically significant

Discussion

Adropin is a peptide secreted from many tissues in our body and has a regulatory role in energy homeostasis, angiogenesis, cell proliferation and cell migration processes (8). In recent years, studies aiming to elucidate the correlation of adropin with various cancers have been conducted. As a result of the literature search, no study investigating the correlation of adropin with gastric cancer was found. Studies have shown that adropin levels change in preprandial-postprandial, obese individuals and patients with diabetes mellutus (20). In order to prevent these conditions from affecting the results, blood samples were taken in a fasting state, and subjects with a BMI >30 and diabetes mellitus were excluded from the study. The mean BMI was similar between the patient and control groups. The results of our study showed that adropin levels were significantly lower in patients with gastric cancer. In a study conducted in patients with endometrial cancer, similar to our study, adropin levels were found to be statistically significantly lower in patients with endometrial cancer compared to healthy individuals (11). It was also shown that adropin levels were lower in the tumour bed in patients with colon cancer, and the relation of adropin administration to these patients with disease progression was investigated. As a result of the study, it was reported that low dose adropin showed antitumour activity by increasing inflammatory activity (9). In our study, the correlation of adropin levels with disease progression, clinical-pathological treatment response and ypT-N stages was examined, but no significant difference was found.

Hypoxia-inducible factor (HIF) regulates the oxygenation of tissues by activating in case of hypoxia and is highly expressed for cancer cells to maintain their viability (21). In gastric cancer, HIF has been shown to increase tumour cell proliferation (22), inhibit apoptosis in tumour cells (23), cause drug resistance (24), increase angiogenesis (25), regulate energy homeostasis by promoting glycolysis (26) and cause tumour progression by these mechanisms. Based on these findings, many anti-cancer drugs targeting HIF in advanced gastric cancer have been tried (27). However, there is no anti-cancer therapy targeting HIF with an acceptable efficacy and side effect profile. In the literature review, the studies focused on patients with advanced gastric cancer and no study was found in patients with gastric cancer who were candidates for neoadjuvant treatment. In our study conducted in patients who were candidates for neoadjuvant treatment, HIF-1α levels were found to be statistically significantly higher than the control group in accordance with

the literature. In the literature, high HIF-1α levels have been shown to be associated with treatment resistance and poor prognosis. In our study, no significant correlation was found between HIF-1α levels and clinical-pathological treatment response, resection status and ypT-N stages.

In locally advanced gastric cancer, R0 resection cannot be performed in approximately 15% of patients with the current standard neoadjuvant treatment, and while the 2-year survival rate of patients is approximately 70%, this rate decreases to 45% in the 5th year (28). Although high curative treatment and long-term survival success is achieved with early diagnosis in many cancer types, unfortunately, the same is not the case for gastric cancer and the unmet need for treatment continues. It is obvious that adropin and HIF-1α are two important factors involved in this process. In addition, adropin and HIF-1α levels differ in patients with gastric cancer compared to the control group and based on this difference, adropin and HIF-1α may be two important parameters for early diagnosis of gastric cancer. Further studies are needed to elucidate the role of adropin and HIF-1α in gastric cancer.

Since our study was designed as a prospective study, the main limitations of our study are the long follow-up periods of the patients included in the study, the relatively small total number of patients due to the fact that some patients left the study and the information of some patients could not be accessed, and the planned number of subgroups could not be reached.

Conclusion

As a result of our study, adropin levels were statistically significantly lower and HIF-1α levels were statistically significantly higher in patients with gastric cancer. No significant difference was found between adropin and HIF-1α levels and various clinical variables such as clinical response, pathological response, operability status, ypT and ypN stages. It was important to demonstrate the relationship between adropin and gastric cancer, which had not been previously investigated and for which no data were identified through a literature review. As evidenced in the literature, HIF-1α has been demonstrated to be elevated in metastatic gastric cancer. This finding was also observed in the early stages of the disease. The present study did not find an association between adropin and HIF-1α and treatment resistance or prognosis. However, the number of patient subgroups was insufficient due to the prospective study design, long follow-up periods, and inability to reach patients who left the study. Further research is required to elucidate the relationship between adropin, HIF-1 alpha, and gastric cancer. This should be conducted with a larger number of patients and longer follow-up periods. It would also be beneficial to investigate the relationship between treatment resistance, recurrence rates, disease-free survival, and overall survival

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