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Effect of hyperemesis gravidarum on maternal renal health: An investigation of the levels of neutrophil gelatinase-associated lipocalin in maternal serum

Hiperemezis gravidarumun maternal böbrek sağlığı üzerine etkisi: Maternal serumda nötrofil jelatinaz ile ilişkili lipokalin düzeylerinin araştırılması

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Abstract

Aim: Hyperemesis gravidarum (HG) is a severe condition that occurs in 0.8–2.0% of pregnant women and can lead to kidney damage. Within minutes of ischemic perfusion injury, renal distal tubular cells release neutrophil gelatinase-associated lipocalin (NGAL). The aim of this study was to assess the levels of NGAL in maternal serum after HG onset and the association between HG severity, renal ischemia, and subsequent kidney damage.

Methods: In this case-control study, the control group comprised healthy volunteers with similar demographic characteristics. The HG patients were divided into three groups according to disease severity based on the Pregnancy-Unique Quantification of Emesis scale as follows: Mild (≤6); moderate (7–12); and severe (≥13). Demographic parameters, biochemical parameters, and serum NGAL levels were compared among the groups.

Results: Serum glucose, serum blood urea nitrogen, serum creatinine, serum phosphorus, aspartate aminotransferase, and alanine aminotransferase levels were similar among the groups. Serum sodium levels were significantly higher in the severe HG group than in all other HG groups. Urine osmolarity was significantly higher in the moderate and severe HG groups than in the control and mild HG groups. There were no differences in serum NGAL levels among the groups.

Conclusion: Our results suggested that serum NGAL levels were not altered in patients complicated by HG.

Keywords: Neutrophil gelatinase-associated lipocalin, Hyperemesis gravidarum, Dehydration

Öz

Amaç: Hiperemezis gravidarum (HG), hamile kadınların %0,8-2,0'ında meydana gelen ve böbrek hasarına yol açabilen ciddi bir durumdur. İskemik perfüzyon hasarı birkaç dakika içinde, renal distal tübüler hücreler, nötrofil jelatinaz ile ilişkili lipokalini (NGAL) serbest bırakır. Bu çalışmanın amacı HG başlangıcından sonra maternal serumdaki NGAL seviyelerini ve HG şiddeti ile böbrek iskemisi ve böbrek hasarı arasındaki ilişkiyi değerlendirmektir.

Yöntem: Kontrol grubu benzer demografik özelliklere sahip sağlıklı gönüllülerden oluşturuldu. HG hastaları Pregnancy-Unique Quantification of Emesis Ölçeğine göre hastalık şiddetine göre üç gruba ayrıldı: hafif (≤6); orta (7-12); ve şiddetli (≥13). Demografik parametreler, biyokimyasal parametreler ve serum NGAL düzeyleri gruplar arasında karşılaştırıldı.

Bulgular: Serum glukoz, serum kan üre azotu, serum kreatinin, serum fosfor, aspartat aminotransferaz ve alanin aminotransferaz düzeyleri gruplar arasında benzerdi. Serum sodyum seviyeleri şiddetli HG grubunda diğer tüm HG gruplarına göre anlamlı derecede yüksekti. İdrar ozmolaritesi orta ve şiddetli HG gruplarında kontrol ve hafif HG gruplarına göre anlamlı derecede yüksekti. Gruplar arasında serum NGAL düzeylerinde anlamlı fark yoktu.

Sonuç: Bulgularımız HG ile komplike olan hastalarda serum NGAL seviyelerinin değişmediğini göstermiştir.

Anahtar kelimeler: Neutrophil gelatinase-associated lipocalin, Hyperemesis gravidarum, Dehidrasyon

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Introduction

It is known that 50–90% of pregnant women between the 4th and 16th gestational weeks experience nausea and vomiting; however, if this becomes severe and requires hospitalization, which occurs in 0.8–2.0% of the women, before the 20th gestational week, the condition is defined as hyperemesis gravidarum (HG) [1,2]. Malnutrition, electrolyte imbalance, and dehydration are the clinical findings associated with HG [4-6]. Sahin et al. [6,7] have reported that severe HG is associated with maternal endothelial dysfunction and increased bone resorption.

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, is a 25-kDa glycoprotein found in human neutrophil granules [8]. Renal distal tubular cells release NGAL within minutes of ischemic perfusion injury and its levels in serum and urine are biochemical markers which can be used to detect very early stages of acute renal injury [9,10]. It has been reported that the plasma concentration of NGAL increases 3-fold within 2 hours of acute renal injury and 10-fold within 3 hours of ischemic injury [11].

Hypovolemia and dehydration are severe complications of HG and cause an elevation in serum blood urea nitrogen (BUN) and creatinine levels in these patients. It has been observed that serum NGAL levels increase much earlier than either BUN or creatinine in the presence of renal ischemic damage, which enables its early detection [9,10]. The primary objective of the present study was to investigate whether there was ischemic damage in renal tubules by assessing the levels of NGAL in maternal serum coinciding with the onset of HG. The secondary objective was to investigate the association between HG severity, the level of renal ischemia, and subsequent kidney damage.

Materials and methods

This case-control study was approved by the Ethics Committee of Erciyes University (decision number: 2019/375) according to the Declaration of Helsinki and was conducted at Kayseri City Hospital, Kayseri, Turkey.

Pregnant patients between their 5th-12th gestational weeks and aged between 18-35 years who were hospitalized due to HG were included in this study. Healthy volunteers with similar demographic characteristics were included in the study as the control group during their routine antenatal visits. The HG patients were separated into three groups according to disease severity, which was determined using the Pregnancy-Unique Quantification of Emesis scale (PUQE). The PUQE scores are defined as follows: ≤6: mild; 7–12: moderate; and ≥13: severe [12].

The diagnosis of HG was made according to the criteria of the American College of Obstetricians and Gynecologists as follows: 1) 5% weight loss from severe nausea and vomiting compared to pre-pregnancy or vomiting more than three times a day and 2) ketonuria with 3–5% weight loss [3]. The exclusion criteria were as follows: Patients with 1) multiple pregnancies, 2) vestibular diseases, 3) hyperparathyroidism or hyperthyroidism, 4) gastroenteritis, hepatitis, bile duct diseases, 5) urinary stones or pyelonephritis, 6) migraine that may cause nausea and vomiting during pregnancy, 7) chronic kidney, liver, or heart diseases, 8) vascular diseases with known renal involvement, or 9) smoking and alcohol use.

Serum NGAL measurement and data collection.

Venous blood samples were collected from each HG study group when as women with severe HG were hospitalized. Blood samples were collected from the healthy volunteers in the control group during their antenatal visit to the hospital in their first trimester of pregnancy. To measure serum glucose, BUN and creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), potassium (K), and sodium (Na) levels, a 4-mL blood sample was collected into a serum separator tube and analyzed the same day in the Kayseri City Hospital biochemistry clinic. To measure serum NGAL levels, a 2-mL blood sample was collected into a serum separator tube, rapidly centrifuged at 10000 rpm for 10 min, and stored in Eppendorf tubes at -80°C until analyses. The collected samples were analyzed using the enzyme-linked immunosorbent analysis method (CUSABIO TECHNOLOGY, LLC; target name: lipocalin 2; code: CSB-E09408h) in the Biochemistry Clinic at Kayseri City Hospital.

Statistical analysis

An analysis of variance followed by Tukey's post-hoc test using Minitab 16 (https://www.minitab.com/en-us/) was used to compare more than two groups. To compare two groups, the Shapiro–Wilk test was used to determine the normality of the data, and the Levene's test was used to test the assumption of homogeneity of variance. The values are expressed as the mean (SD) or n (%). Parametric comparisons were made using the Student's t-test, and nonparametric comparisons were made using the Mann–Whitney U test. The difference among the groups was considered statistically significant when $p < 0.05$. The number of patients in the current study was referred to in a study by Sahin et al. [7]. Accordingly, the 20 volunteers in each group added up to 80 volunteers.

Results

Among 80 participants in the study, 20 were in the healthy control group and 60 were in the HG groups. The participants were divided into three groups according to disease severity as follows: mild HG group (n=20), moderate HG group (n=20), and severe HG group (n=20). Table 1 provides a comparison of the demographic characteristics of the participants. Maternal age, gestational age at blood draw, body mass index, nulliparity, ethnicity, and education levels were similar among all groups (P=0.852, P=0.752, P=0.661, P=0.806, P=0.868 and P=0.907, respectively).

Table 2 provides a comparison of the biochemical measurements among the four groups. Serum glucose (P=0.068), serum BUN (P=0.559), serum creatinine (P=0.595), serum K (P=0.327), AST (P=0.051), and ALT (P=0.063) levels were similar among the groups. Serum Na levels were significantly higher in severe HG group than in the control and other HG groups (P<0.001). Urine osmolarity was significantly higher in the moderate and severe HG groups than in the control and mild HG groups (P<0.001). Serum osmolarity was significantly higher in all HG groups than in the control group (P<0.001). There was no difference in terms of serum NGAL levels among the groups (Table 2, Figure 1).

Table 1: Comparison of maternal demographic characteristics

	Healthy control (n=20)	Mild HG (n=20)	Moderate HG (n=20)	Severe HG (n=20)	*P*-value
Maternal age (year)	28.50 (2.01)	28.30 (2.29)	28.55 (2.70)	28.3 (2.34)	0.852
Gestational age at blood draw (week)	10.6 (1.3)	10.60 (1.5)	10.25 (1.4)	10.8 (3.0)	0.752
BMI (kg/m^2)	24.3 (1.3)	24.4 (1.1)	24.6 (1.3)	24.1 (1.3)	0.661
Nulliparity (n %)	12 (60%)	10 (50%)	12 (60%)	13 (65%)	0.806
Ethnicity Caucasian (n %)	19 (95%)	18 (90%)	19 (95%)	18 (90%)	0.868
Education high school (n %)	8 (40%)	10 (50%)	9 (45%)	10 (50%)	0.907

HG: hyperemesis gravidarum, BMI: body mass index. Values are expressed as the mean (SD) or n (%)

Table 2: Comparison of maternal biochemical results

	Healthy control (n=20)	Mild HG (n=20)	Moderate HG (n=20)	Severe HG (n=20)	*P*-value
Glucose (mg/dL)	92.8 (11.2)	91.2 (9.4)	94.6 (13.5)	86.3 (20.3)	0.068
BUN (5-15mg/dL)	8.43 (2.86)	9.63 (3.46)	9.80 (3.18)	9.78 (4.43)	0.559
Creatinine (0.5–1.1 mg/dL)	0.56 (0.09)	0.55 (0.07)	0.58 (0.08)	0.59 (0.11)	0.595
Na (136–145 nmol/L)	136.1^a (1.5)	136.4^a (2.0)	137.7^b (2.0)	138.3^b (2.0)	<0.001
K (3–5mEq/L)	3.8 (0.2)	3.8 (0.2)	3.9 (0.3)	3.8 (0.2)	0.327
AST (U/L)	12.4 (4.6)	15.7 (7.2)	15.1 (3.1)	16.8 (5.4)	0.051
ALT (U/L)	11.9 (7.1)	14.7 (6.7)	13.2 (7.5)	17.9 (6.8)	0.063
Serum osmolarity (275–295)	282.2^a (2.6)	288.9^a (5.1)	289.8^b (3.1)	289.9^b (2.2)	<0.001
Urine osmolarity (1010–1020)	1012.1^a (6.6)	1020.6^b (7.2)	1024^c (6.2)	1026^c (4.9)	<0.001
NGAL levels (ng/mL)	327.6 (106.9)	296.1 (130.8)	365.1 (118.2)	332.1 (55.1)	0.250

HG: hyperemesis gravidarum, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, NGAL: neutrophil gelatinase-associated lipocalin. Values are expressed as the mean (SD). Different superscripts indicate statistically significant differences

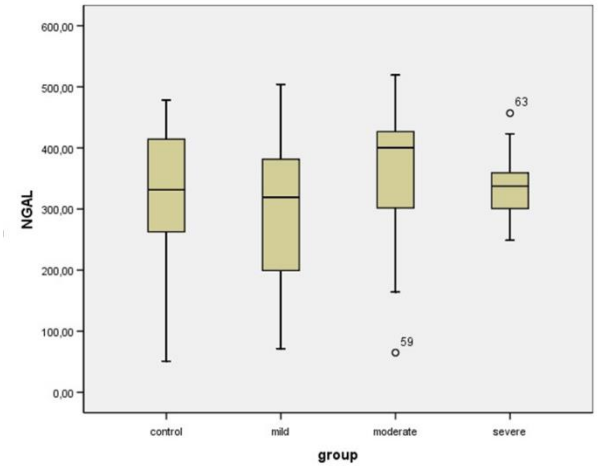

Figure 1: Comparative serum NGAL levels among the four study groups

Discussion

Hypovolemia and dehydration are critical complications of HG that can elevate creatinine levels proportional to disease severity. The aim of our study was to evaluate serum NGAL levels in the presence of HG and investigate the association between disease severity and the levels of renal ischemia.

Although the levels of serum creatinine are widely used to diagnose acute renal failure, it is not an adequate measure of acute renal injury [13] because several factors can regulate these levels, which include its overall generation and its distribution and excretion [13]. With acute renal injury, these levels rise slowly; therefore, new biomarkers must be identified to ensure an early diagnosis. To that end, several authors have evaluated the clinical importance of serum NGAL levels and their connection to dehydration. Antonopoulos et al. [14] have shown that the serum NGAL levels were significantly higher in 12 mildly dehydrated patients than in the healthy controls, 129.4 (25.7) ng/mL and 60.6 (0.4) ng/mL, respectively; however, the leukocyte count, BUN, and serum creatinine levels were not statistically different. Celik et al. [15] have reported that the plasma and urine levels of NGAL in mildly or moderately dehydrated children are higher than those in healthy subjects. It was suggested that these levels can then be used to predict renal impairment in children suffering from mild or moderate dehydration. Tekin et al. [16] have suggested that fasting during long and hot summer days as part of religious practices, such as during Ramadan, leads to fluid deprivation and dehydration, which are related to subclinical maternal renal dysfunction and increased serum NGAL levels.

The results of our study found that serum and urine osmolarity were significantly increased in the moderate and severe HG groups compared to those in the control group, and that serum BUN and creatinine levels were similar among all groups. We did not find any statistical differences in serum NGAL levels among the groups. These results may have been associated with the severity of dehydration and length of time for the disease.

First, it is well documented in the literature that nutritional and metabolic disorders associated with HG severity and prolongation are likely to develop, which increases feto-maternal morbidity [17]. Deficiencies in thiamine, vitamin A, vitamin B6, riboflavin, retinal binding protein, and vitamin K were identified in >60% of HG patients [18]. Wernicke's encephalopathy resulting from thiamine deficiencies [19] and osmotic demyelination syndrome resulting from hyponatremia are other critical metabolic complications [20]. All these complications are related to the extent of HG and occur in patients left untreated. In this study, we included patients who were in the acute period of the disease but who were without metabolic complications.

Secondly, it has been reported that dehydration reduces renal blood flow [14]. During this time, the microvilli of the proximal tubule cells are injured in the prerenal state; however, minimal acute tubular necrosis cannot be detected during this period using routine laboratory tests, such as measuring serum creatinine levels [13]. Prerenal acute kidney injury caused by dehydration may manifest as tubular enzymuria with a concomitant increase in serum NGAL [14]. After examining the pathogenesis of ischemic acute tubular necrosis (ATN), we suggest that patients who become hypotensive after surgery or conditions of sepsis or excess bleeding are at risk of developing ischemic ATN, especially when renal perfusion is either severe or prolonged. In HG patients, inadequate fluid intake activates compensatory mechanisms in response to decreases in renal arterial blood flow and glomerular filtration. These mechanisms provide an adequate volume of blood to vital organs, such as the heart and brain; therefore, we can speculate that these compensatory mechanisms do not adversely affect proximal renal tubule health.

Limitation

Our small sample size is the primary limitation of our study.

Conclusion

The results of the present study showed that serum NGAL levels were not altered in patients with HG.

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