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The Relationship of Kidney Injury Molecule-1 and Interleukin-1 Beta with Hepatic and Renal Functions in Pregnant Women with Thyroid Disease

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ABSTRACT

Introduction: Pregnancy is considered a low-grade inflammatory state presented with increased levels of pro-inflammatory markers. Despite the well-recognized association between inflammation and kidney injury, there is still a lack of available data concerning the role of thyroid hormone alterations in inflammation and acute kidney injury (AKI). We examined the relationship of kidney injury molecule-1 (KIM-1) and interleukin-1 beta (IL-1β) with renal and hepatic injury in hypothyroid, normothyroid (euthyroid), or hyperthyroid pregnant women.

Methods: A total of 77 pregnant women with no additional health problems were enrolled in the study. Serum KIM-1 and IL-1β levels were analyzed by ELISA.

Results: There were significant differences between normothyroid, hyperthyroid, and hypothyroid pregnants regarding creatinine, aspartate aminotransferase (AST), free T4, anti-thyroglobulin (anti-TG), anti-thyroperoxidase (anti-TPO), and plateletcrit (PCT) levels (p=0.018, p=0.032, p=0.011, p=0.001, p=0.003, and p=0.016, respectively). The mean creatinine levels of the hypothyroid group were significantly higher than those of the hyperthyroid group (p=0.015). The mean AST and PCT levels of the hypothyroid group were considerably higher than those of the normothyroid group (p=0.024 and p=0.014, respectively). In the correlation analysis, age was the single parameter that was significantly correlated with KIM-1 and IL-1β in all pregnant women (p=-0.024 and p=-0.018, respectively). In the hypothyroid pregnant women group, KIM-1 was correlated with creatinine levels and age (p=0.037 and p=0.022, respectively).

Conclusion: KIM-1 level in pregnant women with hypothyroidism can serve as a useful biomarker to show AKI.

Keywords: Interleukins, kidney injury molecule-1, pregnancy, thyroid dysfunction

Introduction

The American Thyroid Association recommends thyroid function test screening during pregnancy and the postpartum period to prevent mental-motor growth retardation due to altered thyroid hormone status (1). The impact of overt thyroid dysfunction, which is seen in 2-3% of all pregnancies, is well-known and presents with miscarriage, preterm delivery, mental retardation, pre-eclampsia, or hypertension (2). While 0.2% of pregnant women suffer from hyperthyroidism, the frequency of hypothyroidism may reach 3% but may vary according to age, gestational week, and weight of the pregnant (1,3).

In the guidelines of the American Throid Association, thyroid-stimulating hormone (TSH) <0.1 mIU/mL is used as the diagnostic criterion for hyperthyroidism, 0.1< TSH <2.5 mIU/mL euthyroid, TSH >2.5 mIU/mL hypothyroidism during pregnancy (1). Subclinical inflammation is defined as the presence of increased pro-inflammatory markers without evident clinical findings. Pregnant exhibit subclinical inflammation presented with minimal clinical results along with increased levels of inflammatory parameters. Some studies have determined the relationship of pro-inflammatory cytokines with hypo- or hyperfunction of the thyroid gland (4,5). As proven by human and experimental animal studies, maintaining the normal range of thyroid hormone levels is essential to suppress excessive inflammation (5).

An increasing amount of evidence indicated the association of inflammation with acute kidney injury (AKI) in the general population as well as in pregnant (6). The accumulation of pro-inflammatory cytokines in the glomerulus and altered fluid-electrolyte balance are the main pathogenic mechanisms involved in the inflammation-related kidney injury (7). KIM-1 was proposed to determine renal injury independent of the muscle mass and age of the patient. Besides, plasma levels of KIM-1

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are significantly related to kidney injury in hypertensive or obstructive nephropathy (8,9). Nowak et al. (10) determined the predictive role of KIM-1 in the progression of renal injury of patients with chronic kidney disease.

This study analyzed the relationship of KIM-1 and IL-1β with renal injury and hepatic damage in pregnant women with normo-, hypo-, or hyperthyroidism.

Methods

The study was conducted in the internal medicine outpatient clinics of our hospital. All 205 pregnant women referred between June and July 2019 with suspected thyroid diseases were included. Patients who were already using thyroid medication were excluded. These patients aged between 18 and 30 years without any known disease underwent a detailed physical examination. Demographic features were recorded, and they were divided into 3 subgroups according to the thyroid hormone status. Thirty pregnant (39.0%) had normal thyroid hormone levels, whereas 29 participants (37.6%) had hyperthyroidism, and 18 pregnant (23.4%) had hypothyroidism.

This study approval by the University of Health Sciences Turkey, Bağcılar Training and Research Hospital Ethics Committee (approval number: 2019.05.2.02.046, date: 24.05.2019). All participants provided written informed consent.

Blood samples were collected after 8-hour fasting. Biochemical analyses, including glucose, urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), calcium (Ca), sodium (Na), potassium (K), total protein, albumin, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were performed using spectrophotometric methods in a Siemens Advia 1800 device (Siemens Healthcare Sağlık Co., Turkey). Urinalysis was also performed by the spectrophotometric method in Siemens Advia 1800 device. TSH was analyzed by the chemiluminescence immunoassay method in a Siemens Advia Centaur device (XE-5000, Sysmex Corp. Kobe, Japan). Hemogram parameters were examined in the Cell Dyn Ruby (Abbott Park, Illinois, USA) device using the Multiangle Polarized Scatter Separation method. The glomerular filtration rate (GFR) was measured by the MDRD method. The participants' height and weight were measured using the Tanita Body Composition Analyzer (Tanita Corporation of America, Illinois, USA). Body mass index was calculated as weight/height^2 (kg/m^2). A urine albumin excretion rate exceeding 20 µg/min (30 mg/day), in the absence of uncontrolled hypertension or urinary tract infection, was defined as microalbuminuria. Microalbuminuria was assessed by measuring urine albumin to creatinine ratio.

Serum levels of IL-1 beta and KIM-1 were analyzed by the ELISA using commercially available kits according to the instructions of the manufacturer. Serum specimens and standards with biotin were put into a microtest cartridge coated with antihuman kit antibody. Subsequently, streptavidin-horse radish peroxidase enzyme conjugate was added to the cartridge to remove non-aligned antihuman kit antibody. After incubation, the intensity of the color was spectrophotometrically analyzed at 450 nm wavelength.

Statistical Analysis

In this study, statistical analysis was performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods [mean, standard deviation (SD)] in the evaluation of data, descriptive statistical methods (mean, SD) as well as the normality test were performed using the Shapiro-Wilk test. One-Way analysis of variance in intergroup comparisons of normally distributed variables, Tukey multiple comparison test in subgroup comparisons, Kruskal-Wallis test in intergroup comparisons, Dunn's multiple comparison test in subgroup comparisons, variables in each other. Pearson correlation test was used to determine their relationship, with the results were evaluated at a significance level of $p<0.05$.

Results

There was no significant difference between normothyroid, hyperthyroid, and hypothyroid pregnant concerning the mean glucose, urea, uric acid, ALT, LDH, Ca, Na, K, chlorine, total protein, albumin, total cholesterol, LDL, HDL, triglyceride levels, and hemogram parameters, except PCT (Table 1). Significant differences were determined in creatinine, AST, free T4, anti-thyroglobulin, anti-thyroperoxidase, and PCT levels between the groups (p=0.018, p=0.032, p=0.011, p=0.001, p=0.003, and p=0.016; respectively) (Table 1, 2). The mean creatinine, AST and PCT levels of the hypothyroid group were significantly higher than those of the hyperthyroid group (p=0.015, p=0.024 and p=0.014; respectively) (Table 3).

Serum KIM-1 and IL-1β levels were negatively correlated with the age of the participants (r=-0.258, p=0.024 and r=-0.268, p=0.018, respectively). KIM-1 was significantly related to the mean creatinine and age only in the hypothyroid group (r=0.277, p=0.037, and r=0.251, p=0.022, respectively) (Table 4).

Discussion

This study indicates that hypothyroid pregnant women are more prone to renal injury. In contrast to hyperthyroid and euthyroid pregnant, KIM-1 may show the loss of kidney functions in hypothyroid pregnant. The age of the pregnant women may effect renal injury in patients with hypothyroidism.

Besides the well-known association of thyroid dysfunction with preterm birth, low birth weight, and perinatal death, pregnant with hypo-hyperthyroidism is also more prone to renal injury (11). Although the exact pathogenetic relationship of AKI and hypothyroidism is not well-established, the most probable mechanisms are hypodynamic circulating blood flow and reduced GFR (12). Some case reports have showed that increased creatinine levels return to normal ranges and are maintained by initiating levothyroxine in hypothyroid individuals (13). Although decreased GFR and increased creatinine levels are usually reversible, depending on the chronicity and severity of the hypothyroid state, chronically increased creatinine levels may be seen. Kreisman and Hennessey (13) demonstrated a 35% increase in creatinine levels in 90% of hypothyroid individuals. Similar to the previously mentioned studies,

Table 1. Demographic and biochemical variables between euthyroid, hyperthyroid and hypothyroid pregnant

	TSH=0.10-2.5 euthyroid (n=30)	TSH <0.1 hyperthyroid (n=29)	TSH >2.5 hypothyroid (n=18)	p
Age (year)	28.5±5.75	29.93±6.47	29.5±3.88	0.616
Gestational parity (trimester)	2.67±1.56	2.46±1.45	2.28±1.02	0.769*
Gestational week (week)	18.7±9.32	13.69±6.71	15.83±8.44	0.070
Body mass index (kg/m^2)	26.28±4.88	24.1±4.63	25.73±4.29	0.189
Triglycerides (mg/dL)	151.3±65.71	122.97±83.28	134.83±60.42	0.320
LDL cholesterol (mg/dL)	117.6±51.31	97.28±39.21	118.22±33.55	0.137
Uric acid (mg/dL)	2.77±0.58	2.43±0.59	2.69±0.73	0.109
KIM-1 (ng/mL)	2.98±2.83	3.67±3.46	3.42±3.46	0.703*
IL-β (pg/mL)	1482±1889	1758.±1962	1787±2171	0.306*
Urea (mg/dL)	16.53±4.45	17.49±5.82	16.95±3.5	0.795
Creatinine (mg/dL)	0.54±0.09	0.5±0.07	0.58±0.12	**0.018**
AST (U/L)	14.84±4.58	16.5±4.39	19.63±7.57	**0.032**
ALT (U/L)	13.29±6.54	15.8±11.07	15.59±8.44	0.558
Vitamin D (ng/mL)	9.23±6.85	6.87±4.07	7.79±7.26	0.760*
Free T4 (ng/dL)	1.3±0.55	1.7±0.8	1.17±0.39	**0.011**
Anti-TG (IU/mL)	22.06±44.35	70.01±120.01	62.42±89.07	**0.001***
Anti-TPO (IU/mL)	16.38±22.77	24.95±36.95	114.23±188.11	**0.003***
Glucose (mg/dL)	96.84±23.05	92.49±23.69	89.72±15.9	0.530
Insulin (uIU/mL)	32.8±39.53	18.26±20.15	19.53±21.59	0.082*
HOMA-IR	9.68±16.02	4.92±6.85	5.02±6.78	0.073*

One-Way variant analysis* Kruskal-Wallis test. Significant p-values are shown in bold. TSH: Thyroid-stimulating hormone, LDL: Low-density lipoprotein, KIM-1: Kidney injury molecule-1, IL-β: Interleukin-1 beta, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Anti-TG: Anti-thyroglobulin, Anti-TPO: Anti-thyroperoxidase, HOMA-IR: Homeostasis model assessment of insulin resistance

Table 2. Hematological parameters between euthyroid, hyperthyroid and hypothyroid pregnant

	TSH=0.10-2.5 euthyroid (n=30)	TSH <0.1 hyperthyroid (n=29)	TSH > 2.5 hypothyroid (n=18)	p
Leukocyte (10^3/uL)	9.33±2.66	9.23±2.36	9.56±2.65	0.926
Hemoglobin (g/dL)	11.74±1.18	11.64±1.05	12.07±1.31	0.471
Hematocrit (%)	36.34±3.1	37.28±3.02	37.23±3.13	0.508
Platelet (10^3/uL)	251,600±60,496	250,931±38,030	258,888±38,038	0.840
RDW (%)	13.58±1.47	13.94±1.66	13.58±2.1	0.729
MCV (fl)	87.27±5.52	85.16±5.83	85.76±7.34	0.473
MPV (fl)	7.7±1.61	7.87±1.24	7.96±1.41	0.812
PCT (%)	0.19±0.05	0.21±0.05	0.23±0.06	**0.016**
PDW (%)	20.19±6.16	18.21±3.13	22.01±7.5	0.134
Lymphocyte (%)	22.75±5.47	24.48±5.87	23.25±7.36	0.613
Lymphocyte (10^3/uL)	2.07±0.63	2.23±0.7	2.17±0.83	0.721
Monocyte (%)	5.96±1.92	6.8±1.69	6.27±1.35	0.250
Monocyte (10^3/uL)	0.54±0.19	0.61±0.18	0.61±0.22	0.348
Neutrophil (%)	69.47±6.18	66.85±7.03	68.18±8.37	0.446
Neutrophil (10^3/uL)	6.57±2.34	6.23±1.93	6.56±2.18	0.840

A significant p-value written in bold. TSH: Thyroid-stimulating hormone, RDW: Red cell distribution width, MCV: Mean corpuscular volume, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width

creatinine levels were significantly higher in hypothyroid individuals than in other groups in our research.

Reports regarding hyperthyroidism-induced AKI are scarce (11). Hyperthyroidism-induced renal injury is characterized by increased GFR and reduced serum creatinine, which respond well to antithyroid therapy (7). In contrast to hypothyroidism, tubular or tubulointerstitial damage is the most common pathogenetic mechanism in hyperthyroidism (7). Compared to normothyroid pregnant, the frequency of hyperemesis gravidarum and immune-mediated glomerular diseases are significantly higher in pregnant women with hyperthyroidism, which possesses a risk

Table 3. Pairwise comparisons of the significant variables between the different thyroid categories

Tukey multiple comparison test	Creatinine	AST	Free T4	PCT
Euthyroid/hyperthyroid	0.182	0546	**0.043**	0.169
Euthyroid/hypothyroid	0.388	**0.024**	0.783	**0.014**
Hyperthyroid/hypothyroid	**0.015**	0.194	**0.018**	0.460

One-Way variant analysis. A significant p-value written in bold. AST: Aspartate aminotransferase, PCT: Plateletcrit

Table 4. Correlations of KIM-1 and IL-β with thyroid renal and hepatic function tests in hypothyroid patients

		KIM-1	IL-β
TSH	r	-0.017	-0.037
	p	0.822	0.743
Free T4	r	0.069	0.043
	p	0.589	0.658
Age	r	**0.251**	0.121
	p	**0.022**	0.392
Gestational week	r	0.146	0.179
	p	0.264	0.154
BMI	r	-0.123	-0.083
	p	0.343	0.499
Triglycerides	r	-0.026	0.017
	p	0.845	0.912
LDL	r	0.068	0.099
	p	0.512	0.424
Creatinine	r	**0.277**	0.168
	p	**0.037**	0.301
ALT	r	0.122	0.123
	p	0.301	0.374
Vitamin D	r	-0.068	-0.069
	p	0.541	0.547
Glucose	r	-0.235	-0.241
	p	0.059	0.063

Pearson correlation test. A significant p-value written in bold. KIM-1: Kidney injury molecule-1, IL-β: Interleukin-1 beta, TSH: Thyroid-stimulating hormone, BMI: Body mass index, LDL: Low-density lipoprotein, ALT: Alanine aminotransferase

of acute renal damage (14,15). However, we failed to show an increase in the creatinine levels of hyperthyroid pregnant.

KIM-1 is a relatively recent marker proposed for use in the assessment of renal function in acute injury. It is considered superior to serum creatinine because of its independence from age, gender, and muscle mass (16). KIM-1 is regarded as a regulator of endocytosis in regenerating injured proximal tubule cells, as well as an indicator of the enhanced proliferation of the injured proximal tubules. KIM-1 release into urine precedes proteinuria and decrease in GFR (17). Egli et al. (18) showed no significant association between plasma KIM-1 levels and renal injury in the general population. In this study, although it did not reach statistical significance, KIM-1 levels of hypothyroid and hyperthyroid women were higher than those of normothyroid pregnant. Furthermore, in hypothyroid pregnant, KIM-1 was related to creatinine levels. Thus, KIM-1 level seems to more accurately reflect the increased creatinine level, which shows decreased renal functions.

In a prospective study aiming to evaluate the relationship of KIM-1 with renal functions of pre-eclamptic pregnant, the authors failed to indicate a significant correlation between these variables (19). However, a study conducted in premature infants pointed out that age is a substantial determinant of kidney injury and should be taken into account when evaluating the accuracy of KIM-1 (20). The relationship of IL-1β with the trimester of pregnancy and age of the pregnant are significant predictors of pre-eclampsia related renal injury (21). We found that the relationship of age with KIM-1 and IL-1β was prominent in all patients.

In Mazzaferri and Surks (22) study, the patient's age significantly impacted the manifestations of thyroid dysfunction, including renal injury. Also, in Zhang et al.'s (23) study, the relationship of age with renal injury induced by thyroid dysfunction was remarkable in a population with diabetes. Similar to the literature, we found an association between age and KIM-1 levels in hypothyroid pregnant.

Study Limitations

This study has some limitations like sample size was relatively small and the iodine status of the patients has not been studied. A remarkable number of patients with additional comorbidities or receiving therapy for chronic disorders were excluded. Finally, studying the role of thyroid hormone replacement or antithyroid therapy could provide complementary data on the inflammatory status and renal injury.

Conclusion

In conclusion, to the best of our knowledge, our study is the first report to examine the relationship between serum KIM-1 and IL-1β and thyroid hormone levels in pregnant women. Hypothyroidism is a risk factor for developing AKI during pregnancy, and KIM-1 is an indicator of functional renal loss, especially in pregnant with hypothyroidism. Although the presence of increased inflammation in pregnancies with altered thyroid function is well-established, further studies are warranted to reach a more precise conclusion.

Ethics Committee Approval: This study approval by the University of Health Sciences Turkey, Bağcılar Training and Research Hospital Ethics Committee (approval number: 2019.05.2.02.046, date: 24.05.2019).

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