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Serum fractalkine levels and their association with cardiovascular parameters in patients with overt hyperthyroidism

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ABSTRACT

Aims: Hyperthyroidism is a common endocrine disorder with significant cardiovascular (CV) implications. Emerging evidence links fractalkine to both heart failure (HF) and atherosclerosis. We aimed to compare serum fractalkine levels between patients with hyperthyroidism and healthy controls and to investigate its potential association with CV risk markers.

Methods: This case-control study included treatment-naive adults with overt hyperthyroidism and age- and sex-matched healthy controls with normal thyroid function tests. Participants with cardiovascular disease or major systemic disorders were excluded. All participants underwent physical examination, hormonal profiling, serum fractalkine measurement, electrocardiography, and echocardiographic assessment using both conventional and tissue Doppler techniques to evaluate left and right ventricular function.

Results: The study included 41 treatment-naive patients with overt hyperthyroidism (mean age: 45±12.9 years) and 41 age-matched healthy controls (mean age: 45±8.2 years). Patients with hyperthyroidism had significantly higher serum fractalkine levels than healthy controls (p=0.01). Within the hyperthyroid group, fractalkine levels positively correlated with carotid intima-media thickness (CIMT), a marker of subclinical atherosclerosis (r=0.317, p=0.043), and negatively correlated with mitral annular velocity in late diastole (a'), a diastolic parameter indicative of HF with preserved ejection fraction (HFpEF) (r =-0.344, p=0.028). Linear regression analysis identified fractalkine as an independent predictor of increased CIMT and of reduced a'.

Conclusions: This study demonstrated that fractalkine levels are elevated in patients with hyperthyroidism and are associated with early markers of CV dysfunction, including subclinical atherosclerosis and HFpEF.

Introduction

Hyperthyroidism is a common endocrine disorder with significant implications for the cardiovascular (CV) system. In particular, individuals aged 60 years and older, as well as those with pre-existing cardiac conditions, have been documented to confront an elevated risk of atrial fibrillation (AF), coronary events, and heart failure (HF) in the presence of hyperthyroidism (1). It is noteworthy that studies have underscored the enduring impact of hyperthyroidism on CV morbidity and mortality, persisting up to 35 years post-treatment (2). Despite our current understanding of the CV morbidity and mortality associated with hyperthyroidism, the specific characteristics and outcomes of individual cardiac complications have not been comprehensively studied.

Fractalkine (CX3CL1) belongs to the small-molecule chemokine family known for its ability to induce chemotaxis of myeloid cells (3). It is expressed in various tissues, including the brain, gastrointestinal tract, skin, endothelium, kidney, and lungs. Fractalkine is also expressed on activated platelet surfaces, contributing to macrophage adhesion within atherosclerotic plaques. Emerging evidence underscores its pivotal role in the pathogenesis of specific diseases, such as atherosclerosis and CV conditions, where inflammatory factors play a crucial role (4). Studies have shown that individuals with polymorphisms in CX3CR1, the receptor for fractalkine, exhibit varying degrees of protection against coronary artery disease (5). Thyroid hormone receptors are localized to the plasma membrane of endothelial cells, including integrin $\alpha v\beta 3$. Fractalkine binds to integrin $\alpha v\beta 3$, inducing changes in the physical state of the integrin and activating it (6). The proximity of the binding site to thyroid hormones suggests that thyroid hormones may modulate the effects of fractalkine. Moreover, fractalkine has been shown to have proliferative, anti-apoptotic, and pro-angiogenic effects on the vascular system through its interaction with integrin $\alpha v\beta 3$ (7).

Despite evidence demonstrating a sustained elevated risk of CV disease (CVD) in patients with hyperthyroidism, even after undergoing treatment, the current literature lacks a specific marker indicating the risk of developing CVD attributable to elevated T4 levels in these individuals. Building upon these considerations, our hypothesis suggests that increased T4 levels may affect fractalkine levels and its signaling pathway, thereby contributing to elevated CVD risk. The main objective of the study was to compare serum fractalkine levels between individuals with treatment-naive hyperthyroidism and a control group, emphasizing the exclusion of participants with pre-existing CVD or related risk factors to eliminate confounding. Moreover, our second objective was to investigate potential correlations between serum fractalkine levels and markers of CV abnormalities, assessed by electrocardiography, conventional echocardiography, tissue Doppler echocardiography, and carotid intima-media thickness (CIMT) measurement.

Methods

Study design and setting

The present study was designed as a case-control study and was conducted between March 2021 and March 2022, involving 41 healthy subjects and 41 patients with overt hyperthyroidism. The inclusion criteria for the patient group were treatment-naive, newly diagnosed overt hyperthyroidism and age over 18 years. The control group consisted of age- and sex-matched euthyroid, healthy individuals who met the same exclusion criteria as the patient group. Exclusion criteria included a history of CAD, dysrhythmia, diabetes mellitus, hypertension, structural heart disease, valvular heart disease, anemia, renal and hepatic failure, lung disease, connective tissue disease, and malignancy. None of the participants had used antithyroid medication before enrollment in the study. Additionally, no medications known to affect CV parameters were permitted.

The study involved a comprehensive assessment, including physical examination, hormonal analyses, measurement of serum fractalkine levels, and electrocardiographic (ECG) evaluation. Electrocardiography (standard 12-lead ECG) was carried out for the participants at a paper velocity of 25 mm/s. Changes in left and right ventricular (RV) hemodynamics and performance were assessed by conventional and tissue Doppler echocardiography (TDI). All ECG and echocardiographic analyses were performed by a single observer who was blinded to the study groups. This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Gülhane Training and Research Hospital (approval no: 2021/6, date: 24.03.2021). Written informed consent was obtained from all participants prior to their enrollment in the study.

Laboratory tests

Serum levels of thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were measured using automated immunochemiluminescent assay (ICMA) kits (Roche GmbH, Mannheim, Germany). The coefficients of variation for these thyroid profile assays were below 10%. The reference ranges for TSH, FT4, and FT3 were 0.38 to 5.33 mIU/L, 0.58 to 1.38 ng/dL, and 2.0 to 4.4 pg/mL, respectively. Hyperthyroidism was clinically diagnosed and confirmed by elevated FT4 and/or FT3 levels along with suppressed serum TSH levels. The serum fractalkine levels were assessed using the Human Fractalkine/CX3CL1 ELISA Kit (PicoKine, EK0356) obtained from BOSTER Biological Technology (Wuhan, China). Due to the non-normal distribution of serum fractalkine levels, logarithmic transformations were applied before analysis.

Echocardiographic examination

Echocardiographic measurements in the patients enrolled in the study were obtained using M-mode, two-dimensional, and

color-flow Doppler imaging with a Vivid S60N echocardiography device equipped with a 2.5-MHz transducer. These measurements were conducted by a cardiologist who was blinded to the clinical details of each patient and of the control group, as well as to the results of other examinations. Additionally, tissue Doppler imaging was performed using transducer frequencies of 3.5-4.0 MHz. The spectral pulsed-Doppler signal filters were adjusted until a Nyquist limit of 15-20 cm/sec was achieved, and the minimal optimal gain was applied. Patients were imaged in the left lateral decubitus position at rest. Echocardiographic examinations were performed according to the American Society of Echocardiography guidelines (8).

Left ventricular (LV) systolic function was evaluated using the ejection fraction (EF) calculated according to the Teichholz formula (8). LV diastolic function was assessed by mitral inflow velocities, specifically peak E (early diastolic), peak A (late diastolic), and the E/A ratio. Mitral annular velocities in early diastole (e') and late diastole (a') and the E/e' ratio were also evaluated. All measurements were recorded as the mean of three cardiac cycles. Left atrial (LA) dimension, LV end-systolic and end-diastolic dimensions, diastolic ventricular septal thickness, and diastolic LV PWT were measured in the parasternal long-axis view. LV mass (LVM) was calculated using Devereux's formula (9) and indexed to body surface area (BSA). LV hypertrophy was defined as LVM index (LVMI) >120 g/m^2 for men and >116 g/m^2 for women (10). LA volume was measured using the method of discs in the apical four-chamber view and indexed to the BSA.

RV size was analyzed in the apical four-chamber view by measuring the basal diameter and in the parasternal longitudinal view. RV systolic function was assessed by measuring tricuspid annular plane systolic excursion (TAPSE) and peak systolic velocity (S'). TAPSE, a simple method of estimating RV function, was measured as the difference in the distance between the tricuspid annulus and the RV apex at end-diastole and end-systole of the same cardiac cycle. Tricuspid S' was evaluated by tissue Doppler and measured at the free-wall side of the tricuspid annulus.

Carotid artery intima-media thickness

CIMT was assessed by B-mode ultrasonography using an 18-MHz linear transducer with an Esaote ultrasound device. Measurements were performed with the patients in the supine position and with their necks turned to the opposite side. The standard measurement of CIMT was carried out at a distance of 1 cm from the bifurcation points of the right and left common carotid arteries. During this measurement, the mean right and left CIMT values were calculated and recorded using the available software (Syngo Arterial Health Package). In this study, right and left CIMT measurements were taken 3 times independently, and the results were recorded as averages.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 26.0. Normality was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distributions were expressed as mean ± standard deviation, while categorical variables were presented as frequencies (%). Student's t-test was used to compare means of parametric variables, and the Mann-Whitney test was used for variables with non-parametric distributions. Chi-square tests were used to compare categorical variables. Pearson's test was used for parametric correlations, and Spearman's test for non-parametric correlations. Multiple linear regression analysis was used to assess significant associations of serum log-fractalkine with CIMT and with echocardiographic parameters. A priori power analysis was performed using G*Power 3.1, with an alpha level *(α) of 0.05 and statistical power (1-β) $\underline{\beta}$ of 0.80. The sample size calculation was based on the study's primary endpoints, namely CV parameters [including echocardiographic indices of diastolic function relevant to HF with preserved EF (HFpEF)] and vascular markers such as CIMT, and assumed a moderate-to-large effect size informed by previous studies. Serum fractalkine levels were considered secondary endpoints, and the estimated sample size was deemed sufficient to detect effect sizes comparable to those reported in prior studies on inflammatory biomarkers. Accordingly, a minimum of 40 patients per group was required. A significance level of $p \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics

This case-control study included 41 consecutive patients with overt hyperthyroidism (34 female; 45±12.9 years) and 41 healthy controls (27 female; 45±8.2 years) who met the inclusion criteria. The etiology of hyperthyroidism was Graves' disease (GD) in 90.2% of cases and toxic multinodular goiter in 9.8% of cases. Clinical characteristics such as age, sex, systolic blood pressure, and diastolic blood pressure did not differ significantly between the patient and control groups. Clinical and biochemical parameters differed between the groups, with patients with hyperthyroidism showing lower body mass index (BMI) and levels of serum creatinine, low-density lipoprotein cholesterol, and total cholesterol, as well as higher heart rate, CIMT, and fasting blood glucose compared with controls (Table 1). Additionally, fractalkine was significantly higher in patients with hyperthyroidism (p=0.01) (Figure 1). All the subjects were in sinus rhythm without any significant ST-segment deviation.

Echocardiographic characteristics

All measured echocardiographic parameters were within the reference ranges in all subjects (Table 2). There were no differences between the two groups in LVM, LVMI,

interventricular septal thickness, posterior wall thickness (PWT), LV end-diastolic diameter, and LVEF. The RV systolic function, TAPSE, and Tricuspid S' were significantly higher in the patient group compared with controls (Table 2).

Regarding diastolic function, the patient group exhibited significantly higher values of LA volume index (LAVI), E, and e' (Table 2). Mean E/e' in hyperthyroid patients was 6.53±1.73, which was in the normal range.

Relationship of fractalkine with clinical, metabolic, and echocardiographic parameters

Correlation analyses between fractalkine and clinical, metabolic, and echocardiographic parameters were performed. In the whole group, Fractalkine was positively correlated with CIMT (r=0.301, p=0.006) and FT4 (r=0.251, p=0.023), and negatively correlated with gender (r=-0.270, p=0.014), TSH (r=-0.250, p=0.024), and a' (r=-0.255, p=0.021). In the patient group, fractalkine correlated positively with CIMT (r=0.317, p=0.043) (Figure 2) and negatively with a' (r=-0.344, p=0.028).

We developed a model using linear regression analysis that included age, gender, BMI, and fractalkine to assess CV parameters in the hyperthyroidism group. The model identified fractalkine as a risk factor for increased CIMT and for decreased a' (Table 3).

Table 1. Comparison of characteristics between the hyperthyroid and control subjects

Variables	Hyperthyroidism (n=41)	Control (n=41)	p-value
Age (years)	45±12.9	45±8.2	0.968*
Female, n (%)	34 (82.9%)	27 (65.9%)	0.077*
BMI (kg/m²)	24.54±4.65	27.36±2.75	**<0.001***
BSA (m²)	1.68±0.18	1.82±0.19	**<0.001***
SBP (mmHg)	116.0±12.4	115.3±17.1	0.922*
DBP (mmHg)	81.8±9.6	78.6±7.9	0.240*
Heart rate (beats/min)	86.3±14.9	78.5±9.5	**0.006***
PR (ms)	121.9±23.6	137.02±18.6	**0.002***
CIMT (mm)	0.41±0.05	0.37±0.04	**<0.001***
TSH (mIU/L)	0.005 (0.003-0.007)	1.52 (0.5-4.8)	**<0.001#**
FT4 (ng/dL)	2.25 (0.84-5.31)	0.80 (0.6-1.1)	**<0.001#**
FT3 (pg/mL)	7.61 (2.87-25.27)	3.7 (2.8-4.5)	**<0.001#**
FBG (mg/dL)	90.3 (71-112)	82.7 (65-108)	**0.003#**
Scr (mg/dL)	0.70 (0.5-1.03)	0.90 (0.6-1.1)	**<0.001#**
Total cholesterol (mg/dL)	170.34±33.16	213.83±37.22	**<0.001***
LDL (mg/dL)	95.24± 23.53	135.46±35.43	**<0.001***
Triglyceride (mg/dL)	118.78±57.74	137.90±73.64	0.195*
Log-fractalkine	1.77±0.76	1.39±0.56	**0.010***

*: Student's t-test; #: Mann-Whitney U test
BMI: Body mass index, BSA: Body surface area, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CIMT: Carotid intima-media thickness, TSH: Thyroid stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, FBG: Fasting blood glucose, Scr: Serum creatinine, LDL: Low-density lipoprotein

Table 2. Comparison of echocardiographic parameters between the hyperthyroid and control subjects

Variables	Hyperthyroidism (n=41)	Control (n=41)	p-value
LVM (g)	128.99±24.98	138.51±25.12	0.089*
LVMI (g/m²)	76.71±12.93	76.21±12.83	0.860*
IVST (mm)	8.61±0.95	8.87±0.81	0.172*
PWT (mm)	8.56±0.77	8.75±0.62	0.213*
LVEDD (mm)	44.95±3.13	46.02±2.84	0.109*
LVEF (%)	64.39±2.08	63.53±2.30	0.082*
E (cm/sec)	78.52±22.04	66.48±14.37	**0.005***
A (cm/sec)	74.51±19.45	71.17±14.19	0.377*
E/A ratio	1.12±0.43	0.96±0.28	0.058*
LAD (mm)	31.95±4.26	34.39±3.74	**0.007***
LAVI (mL/m²)	22.00±7.61	18.07±3.93	**0.005***
e' (cm/sec)	12.23±2.59	10.52±2.70	**0.005***

Table 2. Continued

Variables	Hyperthyroidism (n=41)	Control (n=41)	p-value
a' (cm/sec)	10.29±1.83	10.27±1.78	0.282*
E/e'	6.53±1.73	6.58±1.64	0.889*
RVTAPSE (mm)	23.05±2.20	21.75±1.74	**0.004***
Tricuspid S'	12.82±1.37	11.75±1.46	**<0.001***
RV1	29.95±3.83	31.73±5.81	0.106*
RV2	27.0±4.09	26.60±2.91	0.620*
RV3	61.36±6.27	61.92±6.58	0.695*

*: Student's t-test
LVM: Left ventricular mass, LVMI: Left ventricular mass index, IVST: Interventricular septum thickness, PWT: Posterior wall thickness, LVEDD: Left ventricular end-diastolic diameter, LVEF: Left ventricular ejection fraction, E: Early diastolic mitral inflow velocities, e': Early diastolic mitral annular velocity, A: Late diastolic mitral inflow velocities, a': Late diastolic mitral annular velocity, RVTAPSE: Right ventricular tricuspid annular plane systolic excursion, Tricuspid S': Tricuspid lateral annulus systolic velocity, RV1: Right ventricular basal dimension, RV2: Right ventricular mid dimension, RV3: Right ventricular longitudinal dimension, LAD: Left atrial diameter, LAVI: Left atrial volume index

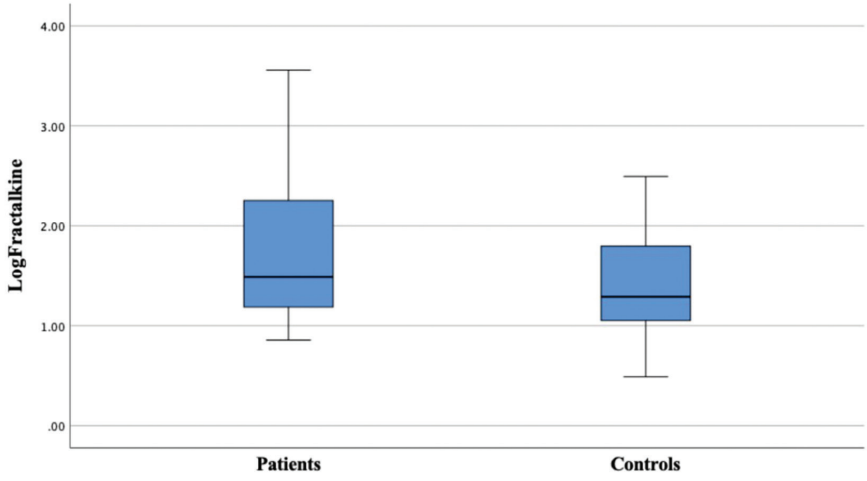

Figure 1. The distribution of fractalkine values in patient and control groups

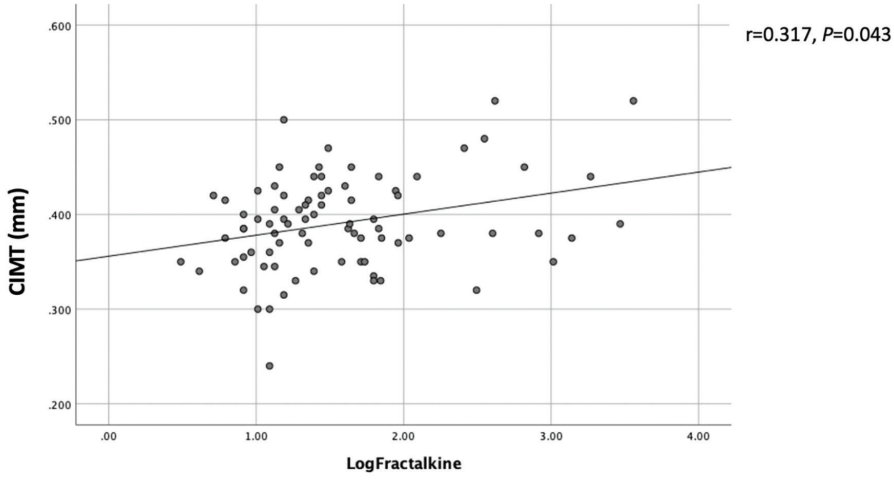

Figure 2. Correlation of serum fractalkine levels with CIMT in hyperthyroidism group
CIMT: Carotid intima-media thickness

Table 3. Relation of fractalkine with cardiovascular parameters in regression analysis

Variables	B	p-value	95% CI
HR	-2.397	0.473	-9.101 to 4.308
CIMT	0.018	0.042	0.001 to 0.038
LVM	1.903	0.682	-7.428 to 11.234
LVMI	0.852	0.765	-4.889 to 6.593
LVEF	-0.685	0.137	-1.598 to 0.228
LAD	0.915	0.291	-0.815 to 2.644
LAVI	-0.152	0.929	-3.592 to 3.289
E	-3.910	0.398	-13.176 to 5.357
A	-3.666	0.374	-11.925 to 4.593
E/A	0.034	0.704	-0.145 to 0.213
e'	-0.525	0.353	-1.655 to 0.606
a'	-0.929	0.019	-1.699 to -0.159
E/e'	0.002	0.996	-0.743 to 0.746
RVTAPSE	-0.537	0.253	-1.474 to 0.400
Tricuspid S'	-0.162	0.600	-0.781 to 0.457

Model including age, gender, BMI, and fractalkine
HR: Heart rate, LVM: Left ventricular mass, LVMI: Left ventricular mass index, LVEF: Left ventricular ejection fraction, E: Early diastolic mitral inflow velocities, e': Early diastolic mitral annular velocity, A: Late diastolic mitral inflow velocities, a': Late diastolic mitral annular velocity, RVTAPSE: Right ventricular tricuspid annular plane systolic excursion, Tricuspid S': Tricuspid lateral annulus systolic velocity, LAD: Left atrial diameter, LAVI: Left atrial volume index, BMI: Body mass index

Discussion

In the present study, serum fractalkine levels were higher in patients with hyperthyroidism compared to controls and were associated with increased CIMT. All echocardiographic parameters were within normal reference ranges; however, certain indices, including TAPSE, Tricuspid S', LAVI, E, and e', were significantly higher in the hyperthyroid group. In this context, our study aimed to assess serum fractalkine levels in patients with hyperthyroidism and to investigate their association with CV parameters in treatment-naive individuals. We observed that higher fractalkine levels were associated with the diastolic parameter a', which has been related to HFpEF. These results suggest that fractalkine may be associated with early CV alterations in hyperthyroidism.

The chemokine fractalkine, also known as CX3CL1, is expressed in a variety of cells, including inflammatory cells, cardiomyocytes, endothelial cells, and smooth muscle cells (11). Possessing leukocyte-chemotactic and vasoconstrictive properties, fractalkine plays a pivotal role in CVD. In 2014, Fujita et al. (6) discovered that the chemokine domain of fractalkine also binds directly to integrin αvβ3 independently of CX3CR1 and thereby activates the integrin. This binding site is near the Arg-Gly-Asp recognition site of integrin αvβ3, proximal to the thyroid hormone-tetrac receptor on that integrin. Consequently, fractalkine may exert integrin-dependent functions in cells lacking CX3CR1 expression. The presence of this chemokine binding site on integrin αvβ3 raises the possibility of interactions between hormone binding and fractalkine binding sites on integrin that may be influenced by high levels of T4 (7). Davis and colleagues have indicated that the regulation of the thyroid hormone receptor on integrin αvβ3 is subject to the expression of fractalkine, a chemotactic cytokine, and its receptor genes (7,12). In our study, we found that serum fractalkine levels were higher in treatment-naive hyperthyroid patients without known CVD than in an age- and gender-matched control group. Consequently, it may be hypothesized that elevated endogenous T4 levels contribute to the development of CVD by enhancing activation of the fractalkine-integrin αvβ3-T4 signaling pathway. However, as fractalkine is not yet an established biomarker in routine clinical practice, these findings should be considered hypothesis-generating and should be validated in larger, prospective studies.

Numerous pieces of evidence support the involvement of fractalkine in CVD (13,14). Husberg et al. (14) were the first to discover an increase in fractalkine protein within the heart tissue of HF patients using western blot analysis. They also noted elevated levels of serum fractalkine in HF patients. In 2019, Ji et al. (15) demonstrated a significant rise in serum fractalkine levels in HF patients compared to healthy individuals, with levels escalating in tandem with the severity of HF. Additionally, they observed heightened fractalkine levels in HF patients who faced readmission within a year (15). Furthermore, Richter et al. (16) reported fractalkine as an independent predictor of mortality in advanced HF patients. In a cohort of AF patients recruited prospectively, Guo et al. (17) established that serum fractalkine independently predicted the risk of major adverse CV and cerebrovascular events. They concluded that lower plasma fractalkine levels were associated with a reduced risk

of such events in AF patients (17). Moreover, Gu et al. (13) employed two models of HF resulting from myocardial infarction and demonstrated that fractalkine neutralizing antibody therapy significantly improved the survival rate of mice. They also discussed the preventive effects of this therapy on cardiac hypertrophy and remodeling post-myocardial infarction (13). Fractalkine-associated pathways contribute to the development and severity of CVDs, suggesting potential for developing treatment strategies that target these pathways. In our treatment-naive hyperthyroid patients, elevated serum fractalkine levels were observed even in the absence of overt CVDs. This finding may suggest an association between fractalkine and early CV alterations; however, its clinical significance remains to be clarified.

It has been demonstrated that approximately 6% of patients with overt hyperthyroidism develop HF (18). Patients with HF are clinically categorized into two groups based on LVEF: those with reduced LVEF (HFrEF) and those with preserved LVEF (HFpEF); 50% of patients fall into the latter category. A recent clinical trial revealed that patients with HFpEF exhibit a prognosis similar to that of those with HFrEF, emphasizing the clinical significance of both categories (19). Oike et al. (20) proposed that a decreased a' during sinus rhythm, serving as an indicator of atrial pump dysfunction, could be a valuable risk marker in HFpEF patients. They demonstrated a higher prevalence of CV and HF-related events in HFpEF patients with low a' levels during sinus rhythm. In our study, LVEF was within the normal range and comparable between the control and hyperthyroid groups. Furthermore, there was no notable difference in the parameter a' between the two groups. However, a statistically significant negative correlation was observed between fractalkine levels and a' in our hyperthyroid patient group, indicating that increased serum fractalkine levels corresponded to lower a' levels.

Since LVEF remains unimpaired in half of individuals with hyperthyroidism-related HF, diastolic dysfunction may also contribute to the development of this condition. However, the studies found controversial results on diastolic function (21-26). Yue et al. (25), who included young hyperthyroid patients in their study similar to ours, found increased diastolic function, as determined by e'. However, they also demonstrated an escalation in diastolic dysfunction associated with advancing age, reaching approximately 100% in individuals aged over 60 years (25), along with a higher BMI (26). No evidence of diastolic dysfunction was observed in either group; however, the parameter e', indicative of LV myocardial relaxation, was notably higher in the hyperthyroidism group. This finding may be explained by the youthfulness of our patient cohort and their lower BMI, which is consistent with existing literature. The increase in diastolic function may be attributed to a compensatory mechanism, which could lead to diastolic dysfunction. However, further studies are needed to validate this hypothesis. No association between fractalkine levels and e' was observed in our study.

There is limited information available regarding the impact of hyperthyroidism on RV systolic function. A simplified measure of RV systolic function, based on RVTAPSE and tricuspid S' may suffice to characterize RV performance. Controversial results were reported on RVTAPSE and Tricuspid S' in hyperthyroid patients (27,28). Some studies reported comparable TAPSE between control and hyperthyroid groups (27), while others reported decreased values (21) or increased values (28). In our study, RVTAPSE and Tricuspid S' were higher in the hyperthyroid group. Similarly, Arinc et al. (28) reported an increase in RV systolic function measured by tissue Doppler imaging. Our findings may once again be explained by a potential compensatory mechanism, observed in young, lean patients without CVD or any discernible risk factors, that may or may not culminate in RV systolic dysfunction. No association was observed between fractalkine levels and RVTAPSE and Tricuspid S' in our study.

Furthermore, we observed increased LAVI in hyperthyroid patients, although values remained within normal reference ranges. Aroditis et al. (21) also noted higher LAVI in Graves' patients compared to controls. However, Shojaeifard et al. (29) reported no significant differences in LAVI between groups. The elevated LAVI values in our patient group, coupled with a prolonged duration of hyperthyroidism, suggest an increased risk of AF. Additionally, our patients exhibited a significantly shorter PR interval, indicating susceptibility to supraventricular arrhythmias. However, our study did not establish a correlation between serum fractalkine levels and either LAVI or PR interval, suggesting no association between fractalkine levels and the risk of arrhythmias.

CIMT, which assesses structural changes in the vascular wall, is a useful noninvasive marker of subclinical atherosclerosis (30). Vascular changes predict CV events independently of CV risk factors such as hypertension or dyslipidemia. In our study, the hyperthyroid group exhibited a statistically significant increase in CIMT compared with healthy controls. The underlying mechanisms of increased CIMT in our patient group, which mainly consists of GD patients, may involve inflammatory and autoimmune processes. The excessive secretion of thyroid hormones and chemokines, such as fractalkine, may contribute to vascular atherosclerosis. Recently, Pettersson-Pablo et al. (31) reported a significant correlation between fractalkine and CIMT in a multivariable model among young healthy adults. Notably, this study is the first to establish a significant relationship between serum fractalkine levels and CIMT in hyperthyroid patients.

Study Limitations

The primary limitations of this study include its cross-sectional, single-center design, relatively small sample size, and lack of prospective follow-up for arrhythmic outcomes. In addition, the absence of quantitative TSH receptor antibody measurements limits our ability to determine whether the observed association between fractalkine and hyperthyroidism is primarily related to elevated thyroid hormone levels or to underlying autoimmune inflammatory processes. Furthermore, the inclusion of both patients with GD and those with toxic nodular goiter may have introduced heterogeneity, as these conditions have distinct pathophysiological mechanisms that could differentially influence the results. Finally, the predominantly female study population may limit the generalizability of the findings.

Conclusion

Our study demonstrated that fractalkine levels were higher in individuals with hyperthyroidism than in controls. In addition, fractalkine levels were associated with CIMT and, a diastolic parameter related to HFpEF. These findings suggest a potential association between fractalkine and CV alterations in hyperthyroid patients. Overall, our results indicate that fractalkine may be associated with CV parameters in individuals with hyperthyroidism.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Ethics Committee of Gülhane Training and Research Hospital (approval no: 2021/6, date: 24.03.2021).

Informed Consent: Written informed consent was obtained from all participants prior to their enrollment in the study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: N.E.G., Concept: N.E.G., Design: Ş.A., N.E.G., Data Collection or Processing: M.A., Ş.A., S.A., Analysis or Interpretation: Ş.A., N.E.G., Literature Search: Ş.A., N.E.G., Writing: M.A., Ş.A., N.E.G.

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