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High cathelicidin levels are associated with Hashimoto's thyroiditis

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Abstract

Aim: Hashimoto's thyroiditis (HT) is a common chronic autoimmune thyroid disease. Many studies on autoimmune diseases have investigated human cathelicidin from the anti-microbial peptide family. This article aims to determine the level of cathelicidin in Hashimoto's thyroiditis and evaluate its relationship with thyroid functions.

Materials and Methods: Eighty-eight subjects were included in the study. Gender, age, and BMI were similar between 48 HT patients and 40 healthy controls. Cathelicidin levels were studied in serum samples with an ELISA kit.

Results: There were euthyroid and subclinical hypothyroid HTs in the study. There was a significant difference between the controls and patients in terms of TSH ($p<0.001$), fT4 ($p=0.001$), anti-TPO ($p=0.001$), and anti-Tg ($p=0.001$). Median cathelicidin level was significantly higher in the HT group (853.53 pg/ml) than in the control group (577.08 pg/ml) ($p<0.001$). Cathelicidin levels were similar ($p=0.555$) in HT with euthyroid and subclinical hypothyroidism. There were no correlations between cathelicidin level and age, year of disease, BMI, TSH, fT4, fT3, anti-TG, and anti-TPO. Diagnosis of HT was approximately 5.6 times higher in patients with high cathelicidin values ($p<0.001$). The possible effect of cathelicidin on the development of HT was evaluated by univariate binary logistic regression analysis, and the diagnostic threshold for cathelicidin was found to be 714 pg/ml (sensitivity 71%, specificity 70%).

Conclusion: Our study is the first to examine the relationship between HT and serum cathelicidin. High cathelicidin was associated with HT independent of thyroid hormone levels, a possible role in the pathogenesis of HT.

Introduction

Hashimoto Thyroiditis (HT) is an autoimmune thyroid disease that progresses with thyroid cell destruction [1]. HT, the most common cause of hypothyroidism in iodine-sufficient countries, is seen in 10% of the general population, the female/male ratio is 10-14/1, and the age of diagnosis is between 30-50 years. The disease is frequently diagnosed with increased TSH, low free T4 (fT4), and high thyroid autoantibodies [2]. In HT, anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg) are determined at a ratio of 90% and 60-80%, respectively [3]. Many studies investigated the relationship between humoral and cellular immune system elements and HT. It is known that cluster of differentiation (CD)4+ T cells play an essential role in the pathogenesis of Hashimoto's thyroiditis (HT), like many autoimmune diseases [4]. In recent years, increased Interleukin (IL) -17 and IL-23 levels, suggesting a relationship between T helper (Th) 17 cells and HT, have been reported in patients with HT [5,6]. IL-22, released from Th17 cells and involved in the chronic inflammatory process, has been suggested to be positively associated with anti-TPO titers [7]. Moreover, increased IL-17 secretion is associated with inflammatory thyrocyte destruction and hypothyroidism in HT [8].

Human cathelicidin (LL-37) is a member of the anti-microbial peptides (AMP) from the immune system elements that have immune modulator effects in host defence [9]. Human cathelicidin encoded on chromosome 3 has anti-microbial, apoptotic, cytotoxic, and chemotactic activity [10]. Apart from the immune response against microorganisms, cathelicidin plays a role in tissue homeosta-

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sis, regenerative processes, and the regulation of inflammatory responses [11]. In recent years, it has been emphasized that cathelicidin's immunomodulatory effects may be pro-inflammatory and anti-inflammatory. It is thought that cathelicidin produced by neutrophils is a potent inducer of inflammatory cytokines that promotes the development of autoimmune responses and that cells targeted by autoimmunity synthesize cathelicidin as a defender [12]. The efficacy of cathelicidin is dose-dependent and performs its immunomodulatory effects at lower concentrations [13].

In the literature, there are in-vivo and in-vitro studies of cathelicidin in autoimmune and inflammatory diseases such as Behçet's disease [14], familiar Mediterranean fever [15], Crohn's disease [16] and ANCA-associated vasculitis [17]. Cathelicidin was positively associated with disease severity in psoriasis [18] and negatively correlated with disease activity in patients with SLE [19]. Very few studies on the level of cathelicidin in autoimmune endocrine diseases exist. The patients with type 1 diabetes had high serum cathelicidin levels and their association with microangiopathy [20].

When naive CD4 T cells are activated, they become groups of effector T cells with different functions. Th17 cells are the subgroup responsible for inflammatory activation and autoimmunity [21]. IL-17A, IL-17F, and IL-22 are increased by induced Th17 cells [22]. CD4+ Th cells are essential in tissue destruction in many inflammatory and autoimmune diseases, including HT [23,24]. Cathelicidin influences the frequency and specificity of cytokine production from Th17 cells. With cathelicidin exposure, IL-17 production from Th17 cells increases approximately sixfold [25].

Taken together, we aimed to investigate the possible relationship between serum cathelicidin level as an immune modulator associated with the cytokine production from Th17 cells leading to hypothyroidism in patients with HT.

Materials and Methods

Subjects

This study was designed as a single-centre cross-sectional study. Both newly diagnosed and followed-up patients who applied to the endocrinology outpatient clinic within three months were included. Patients were grouped according to their thyroid hormone levels at admission. The study was conducted according to the Declaration of Helsinki principles, and approval was obtained from the local ethics committee for this study protocol (Gazi University Clinical Research Ethics Committee, 25.12.2017/620). All patients signed written consent forms before enrollment in the study. Eighty-eight subjects were included in the study; 48 with HT were admitted to the Department of Endocrinology and Metabolism, and 40 were age- and sex-matched healthy controls. The diagnosis of HT was confirmed by the presence of anti-TPO and/or anti-Tg antibodies and/or previous records of thyroid ultrasonography with an ultrasound pattern of thyroiditis. Those with other acute or chronic diseases, infections, and Vitamin D deficiency in HT patients were excluded from the study. Healthy controls were selected from those without acute or chronic disease, infections, or vitamin D deficiency. Based on similar studies, the number of patients was determined by G power analysis.

Assays

Demographic data were recorded. TSH, fT3, fT4, Anti-TPO, and Anti-Tg levels were recorded using Beckman Coulter branded chemiluminescence immunoassay method kit. TSH 0.38-4.00 mIU/ml, fT4 0.61-1.12 ng/dl and fT3 2.6- 4.37 pg/ml were considered the reference values; Anti TPO> 9 IU/ml, Anti Tg> 4 IU/ml were evaluated as positive. After an overnight fast, 10 ml blood samples were taken from each patient and delivered to the Biochemistry Department. Here, samples were rapidly centrifuged to obtain plasma and frozen, stored at -80°C until analysis. Stored serum samples were studied with the CAMP (Cathelicidin Anti-microbial Peptide) ELISA kit branded Cloud-Clone Corp, coded SEC419Hu, and lot number L180109452 results were evaluated. The detection range for cathelicidin was from 125 pg/ml to 8000 pg/ml.

Statistical analysis

The data were analyzed using commercial statistical software, which is the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA). The descriptive statistics section gave categorical variables as numbers and percentages. The conformity of continuous variables to normal distribution was evaluated by Shapiro-Wilk test, while the homogeneity of variance was evaluated by Levene's test. Continuous variables were presented with the median (minimum-maximum) for data that did not show normal distribution. Pearson chi-square test, Fisher Chi-square test, and Continuity Correction chi-square test were used to compare categorical variables between independent groups. Kruskal-Wallis test was used to test the significance of the difference between three or more groups in non-normally distributed independent sample groups. The Mann-Whitney U test with Bonferroni correction was used as a post-doc test to analyze the paired groups (Bonferroni-corrected $p < 0.05/3 = 0.0167$). Spearman Rho correlation analysis was used to examine the relationship of LL37 with some demographic data and laboratory results. ROC (Receiver Operating Characteristics) analysis was performed to determine whether cathelicidin values had a cut-off value useful in distinguishing patients with HT. Sensitivity, specificity, positive, and negative predictive values of limit values with significance levels were calculated. The impact of cathelicidin on HT was analyzed by univariate binary logistic regression analysis. P values below 0.05 were considered significant.

Results

Positive anti-TPO Abs were present in all 48 patients (100%) as an inclusion criterion, while positive anti-Tg Ab was seen in 20 patients (41.67%). There was no difference between the control and patient groups in terms of gender (p=0.913), age (p=0.913), and BMI (p=0.304), fT4 (p=0.471), fT3 (p=0.289). There was a significant difference between the control and patient groups in terms of TSH (p<0.001), anti-TPO (p<0.001), and anti-Tg (p< 0.001) (Table 1).

Table 1. Clinical and biochemical characteristics of HT patients and healthy controls.

	HT(n:48)	Control (n:40)	p
Gender (female)	44 (91.7%)	36 (90%)	0.787
Age (year)	32 (18-59)	32.5 (19-56)	0.913
BMI (kg/m^2)	23.85 (18.5-40.5)	23.65 (16.3-31.0)	0.304
TSH (mIU/ml)	3.31 (0.56-15.70)	1.60 (0.57-3.70)	**<0.001**
fT4 (ng/dl)	0.89 (0.61-1.08)	0.86 (0.62-1.12)	0.471
fT3 (pg/ml)	3.26 (2.61-4.10)	3.33 (2.77-4.20)	0.289
Anti TPO (IU/ml)	391.95 (23.7-5222)	0.5 (1-5.3)	**<0.001**
Anti Tg (IU/ml)	2.80 (0.9-2262)	0.9 (0.3-3.4)	**<0.001**
Cathelicidin (pg/ml)	853.53 (528.42-1534.65)	577.08 (292.77-1474.43)	**<0.001**

The Chi-square test or Mann-Whitney U test was used according to distribution normality.

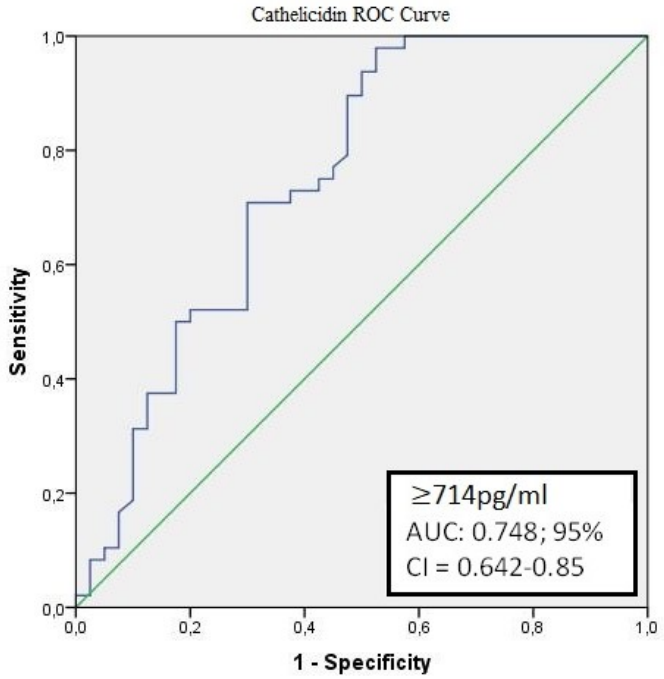

Figure 1. ROC curve analysis of cathelicidin for the risk of Hashimoto's thyroiditis.

Of the subjects, 37.5% (n:18) of HTs were newly diagnosed, and 62.5% (n:30) were followed up. The median follow-up period of the patients was six years (2-20). Six (20.0%) of the patients with follow-up were not receiving levothyroxine treatment. Twenty-four (80.0%) of the patients with follow-up were receiving LT4 replacement therapy, and the median LT4 dose was 75 mcg (50-200). When the patients were grouped as newly diagnosed and followed-up, there was no difference between newly diagnosed and followed-up groups regarding gender (p=0.59), age (p=0.254), BMI (p=0.932), fT3 (p=0.183), fT4 (p=0.831), TSH (p=0.840), anti-TPO (p=0.523), and anti-Tg (p=0.330). 72.2% of newly diagnosed patients were euthyroid and 27.8% were subclinical hypothyroid. In the follow-up patients, 63.3% were euthyroid and 36.7% were subclinical hypothyroid. Despite the replacement therapy, 26.6% of follow-up patients had subclinical hypothyroidism. No patients with clinical hypothyroidism were observed.

In our study, the lowest cathelicidin level was 292.77 pg/ml, and the highest was 1534.65 pg/ml. The median value of cathelicidin was 577.08 (292.77-1474.43) pg/ml in the control group and 853.53 (528.42-1534.65) pg/ml in the HT group; it was higher in patients with HT (p<0.001). When the patient group was evaluated according to the age of diagnosis, cathelicidin was higher both in the new diagnosis (895.21 (528.42-1534.65) pg/ml, p< 0.001) and follow-up (809.07 (557.62-1472.29) pg/ml, p<0.001) groups compared to the control group. Cathelicidin was higher in newly diagnosed patients than in the follow-up patients, but there was no statistical difference (p=0.160).

Cathelicidin was higher both in the euthyroid (857.94 (557.62-1534.665), p<0.001) and subclinical hypothyroid (835.22 (528.42-1362.97), p=0.010) groups compared to the control group. However, cathelicidin levels were similar (p=0.555) in HT with euthyroid and subclinical hypothyroidism (857.94 (557.62-1534.65) vs (835.22 (528.42-1362.97) pg/ml).

There was no correlation between Spearman's rho correlation test and cathelicidin level and age, disease age, BMI, TSH, fT4, fT3, Anti-TG, Anti TPO, and LT4 treatment dose in all groups. As a result of the evaluation with ROC analysis, cathelicidin was found to have a diagnostic value in predicting HT (AUC: 0.748; 95% CI = 0.642-0.85; p <0.001, Figure 1); The diagnostic threshold was 714 pg/ml (sensitivity 71%, specificity 70%). When all the cases were evaluated, the diagnosis of HT was approximately 5.6 times higher in patients with high cathelicidin values (≥714pg/ml) (p<0.001).

Discussion

In the present study, we found that high serum cathelicidin levels were highly associated with HT; moreover, it seems that euthyroidism or subclinical hypothyroidism has no effect on the levels of cathelicidin. Although there are many studies on the relationship of cathelicidin with CD4+ T and Th17 and its effect on the pathogenesis of autoimmune diseases, no studies are focusing directly on the relationship between cathelicidin and HT. Our study sheds light on this issue.

It performs the immune modulator effects of cathelicidin in lower concentrations than its anti-microbial effects [26]. In the literature, in studies investigating serum cathelicidin levels in autoimmune diseases such as psoriasis and

Crohn's disease, it was observed that the cathelicidin level remained in the lower 1/3 according to the kit reference range studied [16,27]. The detection range of the cathelicidin ELISA kit, which was also used in our study, was 125 pg/ml -8000 pg/ml, the maximum cathelicidin values were 1534.65 pg/ml, and the median value was 853.53 pg/ml in the HT group. Our study showed that cathelicidin level remains in the lower 1/3 of the kit range in HT. Namely, HT has a low concentration of cathelicidin positivity, which is similar to other autoimmune diseases and contrary to antimicrobial results.

Hidradenitis suppurativa (HS) is an inflammatory skin disease, and the pathogenesis of the disease has attracted attention for many years. Thomi et al. In 2017, it was determined that increased cathelicidin in HS correlated positively with pro-inflammatory cytokines associated with the Th1/Th17 pathway [28]. This was related to increased CD4 T cells induced by increased calcium signalling after the cathelicidin increase. This study shows the relationship between cathelicidin and autoimmune diseases [28]. When the relationship between HT and IL-17 and IL-23 was investigated, IL-23 and IL-17 were higher in all groups of HT (euthyroid, hypothyroid, and treated) compared to the control group. In addition, when the patient group was evaluated, there was no difference in cytokine levels between the euthyroid, hypothyroid, and treated groups and no correlation was observed between cytokine levels and ani-TPO. In our study, cathelicidin showed a similar course with IL-23 and IL-17 [29]. Hashimoto's thyroiditis is known to manifest as a silent disease, often remaining asymptomatic and without causing hypothyroidism for many years [2]. The patients, identified as newly diagnosed in this study had not previously sought medical attention for any clinical symptoms, and they were found to have antibody positivity and chronic thyroiditis findings through ultrasonography for the first time. Our study aimed to investigate the impact of both the follow-up period and treatment on cathelicidin levels by including newly diagnosed patients as well as follow-up patients. Although cathelicidin was higher in newly diagnosed patients than in follow-up patients, this difference was not statistically significant. Cathelicidin was higher in both newly diagnosed and follow-up patients than in controls.

In the study, euthyroidism was achieved in some patients with replacement therapy, but some patients were euthyroid without treatment, which may complicate the interpretation of the relationship between thyroid hormone status and cathelicidin level. Cathelicidin levels were similar between the euthyroid and subclinical hypothyroid HT groups but higher than the control groups. Similar to IL-17 and IL-23, this situation may be evidence that cathelicidin has an immunological role in the development of HT independent of other factors [29].

Age and gender are shown to be among the factors affecting serum cathelicidin levels in rat studies in the literature [30]. However, no significant correlation was found between cathelicidin level and age, disease age, BMI, thyroid hormone status, thyroid autoantibodies, and treatment dose in our patients with HT.

In our study, anti-TPO positivity was 100%, and anti-Tg positivity was 41.67%. Studies show a negative relationship between anti-Tg positivity and disease age [31]. Our study thought that the low number of newly diagnosed HT patients decreased the probability of detecting anti-Tg positivity. Although thyroid antibodies are associated with inflammation and disease activation in the thyroid gland, there is no clear relationship between thyroid autoantibody titer and hypothyroid severity [2]. Cathelicidin also showed similar behaviour with thyroid autoantibodies; when serum cathelicidin levels were compared in patients with euthyroid and subclinical hypothyroid HT, no significant difference was found between the groups.

The limitation of our study was that not all patients were newly diagnosed and untreated. In addition, the absence of clinical hypothyroidism in patients made it difficult to explain the relationship between cathelicidin and thyroid hormone levels. Our study was planned as cross-sectional, and all HT patients who met the criteria in the three months were included, regardless of thyroid hormone status and replacement dose. Heterogeneity occurred in the patient group due to the study design. Despite this, cathelicidin levels were found to be higher in all patient groups than in the control group. No correlation was found between cathelicidin level and thyroid hormones and replacement dose. In addition, the risk of HT increases 5.6 times at cathelicidin levels above the cut-off value determined by sensitivity 71% and specificity 70%. This indicated that cathelicidin is involved in the pathogenesis of HT and suggests the presence of disease independent of other conditions.

Conclusion

In conclusion, our study is the first to examine the relationship between HT and cathelicidin, which is known as an immunomodulatory peptide. High serum cathelicidin was found in patients with HT regardless of thyroid hormone levels and time of diagnosis.

Ethical approval

Ethical approval was obtained for this study from Gazi University Clinical Research Ethics Committee (25.12.2017/620).

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