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ORIGINAL ARTICLE

The Influence of Overt Hyperthyroidism on the Plasma Level of β- type Natriuretic Peptide

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KEYWORDS

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ABSTRACT: Thyroid hormones (THs) have different effects on the heart and peripheral vascular system. Several changes occur across different status of thyroid dysfunctions. Overt hyperthyroidism (OHyper) induces significant changes in cardiac functions. Untreated OHyper is a cause of heart failure (HF). B-type Natriuretic Peptide (BNP) synthesized primarily in the myocardium. Thus, it is recommended as a diagnostic and prognostic marker for patients with HF. The present study was conducted to measure the effects of OHyper on the BNP level. A case-control study was conducted at a private clinic; Mosul Daily Surgical Clinic, Mosul, Nineveh, Iraq. From 1st Oct., 2020 to 1st Mar., 2021. Thirty (30) apparently healthy subjects with normal thyroid functions; Euthyroid (EU) subjects regarded as control group. Another newly diagnosed thirty (30) OHyper patients were enrolled in this study after exclusion of any facts that affect BNP level as cardiac disease, hypertension, patient taking angiotensin converting enzyme inhibitor, and pregnant ladies. They were diagnosed on the basis of thyroid function tests (TFTs); Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (FT3) and Free Thyroxine (FT4). Plasma level of BNP were measured in OHyper and EU subjects' group. Plasma BNP level is higher in patients with OHyper than EU individuals with mean values of 27.40± 35.59 and 21.68± 28.57 pg ml^{-1}, ($p>0.05$) respectively. Moreover, there was a positive correlation between plasma BNP and serum FT4 level in EU ($r=0.31$, $p=0.01$) and in OHyper patients ($r=0.57$, $P=0.001$). OHyper affect plasma BNP level possibly influencing the secretion of this peptide. Therefore, thyroid functions have to be considered when evaluating any high plasma BNP level.

INTRODUCTION

Thyroid hormones (THs) have different effects on the heart and peripheral vascular system [1-4]. The cardiovascular system (CVS) is the target system for the action of THs, especially T3 through the direct effects on the vascular smooth muscle [5-6]. Several changes can occur in different status of thyroid dysfunctions [1-3]. In patient with Overt Hyperthyroidism (OHyper) owing to a decrease in systemic vascular resistance (SVR), these include an increased heart rate, preload contractility and cardiac output [7-8]. The combination of these factors can lead to a hyperdynamic circulation [9-10]. The increase in heart rate and cardiac output, despite normal level of catecholamine's, is due to the role of THs in the regulation of many ionic membrane transporters such as Na/K ATPase, Na/Ca exchanger and the voltage-dependent K channels [11-12]. As a result of decrease in SVR, the renin –angiotensin –aldosterone system is activated and sodium /water retention occur in patients with OHyper [13]. Untreated OHyper is a leading cause

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of heart failure (HF) which associated with increased morbidity and mortality [14-15].

In 1988, a peptide was purified from the porcine brain; it was named “Brain Natriuretic Peptide” [16]. later on, this peptide known as” B-type natriuretic peptide” (BNP) and it was discovered to be synthesized primarily in the myocardium [17-18]. BNP is synthesized as a 134 amino-acid ‘pre-proBNP’, which is cleaved to ‘proBNP’, a further processing give rise to the inactive N-terminal pro-BNP (NT-proBNP) (76-residues) and the biologically active C-terminal BNP (32-residues) [19]. BNP belongs to the natriuretic peptide family that have different physiological effects, including diuretic, natriuretic, and vasorelaxant actions [20-21]. Excessive stretching is the main stimulus triggering the secretion of BNP by the ventricular myocytes [22], rather than the trans-mural pressure load [23-28]. It was noted that FT3 has a direct stimulus for the BNP secretion from myocardial cells through increasing the gene expression [29-30]. It acts as a blood pressure regulatory hormone that is physiologically oppose and suppress the renin-angiotensin aldosterone system, endothelin-1, and the sympathetic nervous system [31]. Thus, it is considered as a cardioprotective peptide [32]. An increase of heart rate, total blood volume, left ventricular end-diastolic volume and cardiac output in hyperthyroidism exerts a “stress” effect on the cardiac wall. A possible stimulus for the secretion of BNP, and subsequently increased plasma BNP level [33]. Plasma BNP level has been recommended as diagnostic and prognostic marker for the patient with HF [34-37].

MATERIALS AND METHODS

A case-control study conducted at a private clinic, Mosul Surgical Daily Clinic, Mosul, Nineveh, Iraq from 1st Oct, 2020 to 1st Mar, 2021. All participants in the study asked for their permission to be enrolled in this study and their consents were obtained after explaining the idea of the study. A questionnaire was fulfilled by each participants including the followings: name, age, sex, weight, height, BMI, history of diseases (hypertension, arrhythmia, diabetes mellitus, goiter and skin disorder), type of salt used and blood pressure (BP) were recorded. After the selection and inclusion of the participants in the study group, thirty apparently healthy subjects with normal thyroid functions; Euthyroid (EU) subjects regarded as a control group, consisted of twenty-six females and four males, their ages between 18-69 year. With serum TSH, FT3 and FT4 levels within the normal reference ranges. Another thirty newly diagnosed OHyper patients were enrolled in this study after exclusion of any fact that affect BNP level as cardiac diseases, hypertension, patient taking angiotensin converting enzyme inhibitor, and pregnant ladies. These patients consisted of twenty-five females and five males; their ages ranged between 17-68 year. They were diagnosed on the basis of thyroid function tests (TFTs): thyroid stimulating hormone (TSH), reference range (RR):0.38-5.33 µIU ml^{-1}, Free Triiodothyronine (FT3), RR:4.3-6.9 pmol l^{-1}, and Free Thyroxine (FT4), RR:7.85-14.42 pmol l^{-1}). Therefor OHyper was defined by serum TSH level below 0.38 µIU ml^{-1} also increased serum FT3 level more than 6.9 pmol l^{-1} and increased serum FT4 level more than 14.42 pmol l^{-1}. For the plasma level of BNP was measured in both subject groups (normal range: ≤26.5 pg ml^{-1}).

A venous blood of about five milliliter (ml) was taken from each subject in both groups. Two ml of blood were put in EDTA tube to assess BNP level, after shaking for half minute, then centrifugation in order to obtain a plasma sample for measurement of BNP by Tosoh AIA-360, Tokyo, Japan through Immuno Enzymometric Assay [38]. Another three ml of blood put in a gel tube is used for TFTs estimation. Centrifugation was done to obtain serum, through Access 2 (Beckman coulter), NHANES, USA [39] using an electro chemiluminescence (ECL) technique.

Approval of the study was obtained from the Committee of Ethics at Nineveh Health Directorate, Mosul, Iraq.

Statistical analysis

Descriptive statistical methods were used to summarize and tabulate data. T-Test was performed for the two independent samples to assess the significance of differences in continuous variables between euthyroid and OHyper group. Data were expressed as a mean with standard deviation (SD), P-values <0.05 were considered a statistically significant. Pearson correlation test was used to assess the strength and direction of relation between BNP and FT3, FT4 and TSH level. Linear regression test assesses the percentage of changes in BNP is due to unit changes in thyroid tests. The test was also used for curve estimation and formulate prediction equation of BNP based on thyroid test in health and disease status. All statistical procedures were performed using IBM SPSS (Statistical Package for Social Sciences) statistics for windows version 26.0 (Armonk, Ni/: IBM corp).

RESULTS

Clinical and biochemical characteristics of the subjects with OHyper and EU are summarized in Table1which shows a significant difference between the mean values of weight, body mass index (BMI), systolic BP,FT3,FT4, and TSH for EU versus OHyper. In contrast, no significant differences between the mean values of age, height, and diastolic BP of both groups. FT3, FT4 and TSH distribution values showed a significant difference between the two groups. But no statistically significant differences between the distribution values for the BNP in patients with OHyper (27.40±35.59) and that of EU subjects (21.68±28.57). No significant correlation was found in both groups between (FT3 and BNP) and (TSH and BNP) as shown in Figure 1 and Figure 2, respectively. While a significant positive correlation was found between FT4 and BNP in EU (r=0.31, p=0.01) and OHyper (r=0.57, p=0.001) is illustrated in Figure 3.

Table 1. Clinical and biochemical characteristics of OHyper patients and EU subjects.

Variables	**Euthyroid**	**OHyper**	**Difference**	**P-value***
	Mean±SD	**Mean±SD**	**Mean±St error**	
Age	38.33±14.401	39.37±12.713	-1.03±3.50	NS
Weight, kg	79.50±15.828	70.96±14.513	8.54±3.92	0.03
Height, cm	160.70±8.142	159.30±6.974	1.40±1.95	NS
BMI, kg m$^{2-1}$	30.85±6.776	28.06±5.866	2.79±1.63	NS
Systolic BP, mmHg	120.00±8.710	123.67±7.184	-3.66±2.06	NS
Diastolic BP, mmHg	78.00±5.509	76.83±8.659	1.16±1.87	NS
FT3, pmol l^{-1}	4.21±0.560	12.30±11.414	-8.09±2.08	0.001
FT4, pmol l^{-1}	13.53±3.279	28.70±15.215	-15.17±2.84	<0.0001
TSH,	1.77±1.240	0.020.06	1.75±0.24	<0.001
BNP, pg ml^{-1}	21.68±28.57	27.40±35.59	-5.72±8.47	NS

*P-value by two independent samples t-test

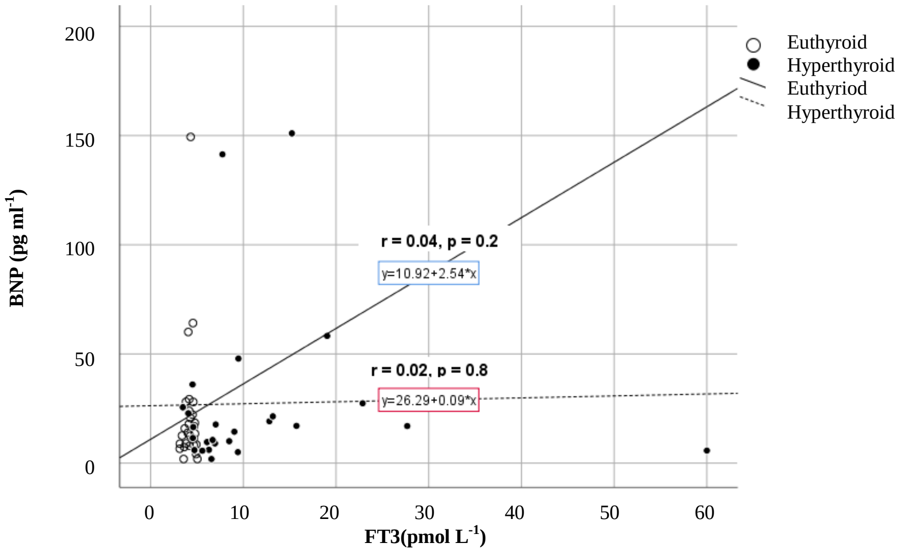

Figure 1. BNP versus FT3(Pmol L^{-1}) in OHyper Patients and Eu subjects.

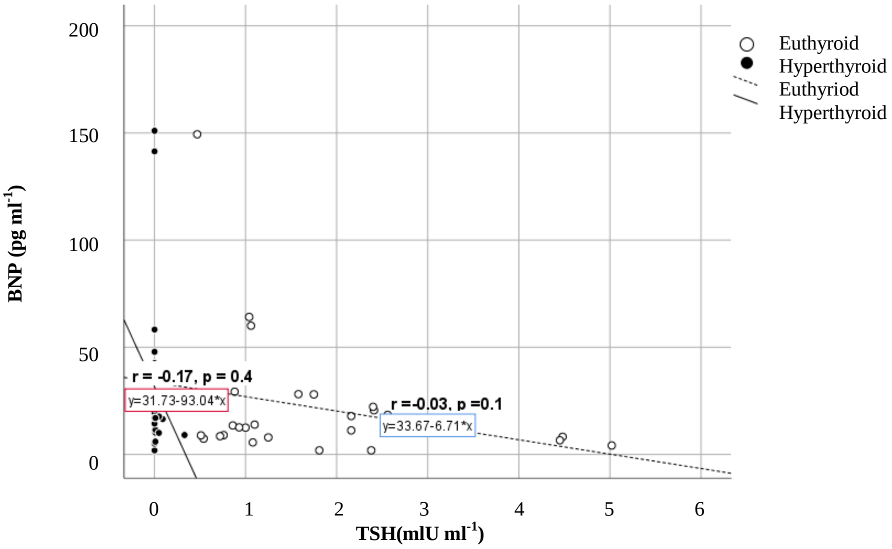

Figure 2. BNP versus TSH (µIU ml^{-1}) in OHyper Patients and Eu subjects.

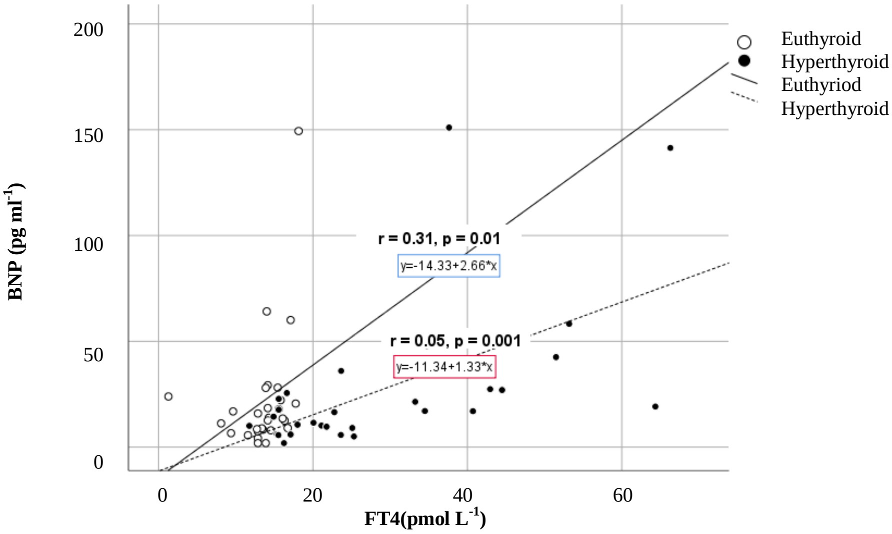

Figure 3. Scatter plots of BNP versus FT4(Pmol L^{-1}) in OHyper Patients and Eu subjects.

DISCUSSION

THs play a central role in the homeostasis of CVS. Regulation of several process related to maintain heart structure, electrophysiological functions and cardiac contractility [40]. Several changes can occur in different status of thyroid dysfunctions [1-3]. THs cause several hemodynamic changes, these include increase myocardial contractility, cardiac output and a decrease in SVR [41]. This Lead to myocardial stretching, through genomic and non-genomic pathways [42,43] therefore thyroid dysfunctions can contribute to the pathogenesis of HF [1]. BNP released from ventricular myocardium in response to myocardial stretch [22], moreover THs increase directly the myocardial gene expression of BNP [30]. BNP levels highly associated with the severity and prognosis of HF [44]. Our results showed that the distribution value for the BNP in patients with OHyper is different from that of EU subjects but it doesn’t reach the statistical significance level. Thus, the result of this study was in accordance with that of Kohno and his colleagues at 1993 [46], whom found an increased BNP levels in OHyper patients compared to the EU subjects. Ertugrul and his colleagues at 2008 [26] evaluated BNP levels in patients with OHyper and EU subjects, they reported that BNP levels were higher in OHyper patients than that of EU subjects.

In contrast Özmen et al.,(2007), showed a significant higher level of NT-proBNP in hyperthyroid patients than in EU subjects [45]. The probable cause for this difference could be due to the way of assessment used by the mentioned study, they used ECL immunoassay [44], which is more sensitive method than immuno enzymometric assay used for measurement of BNP in this study.

A significant positive correlation was found between FT4 and BNP in EU (r=0.31, p=0.01) and OHyper (r=0.57, p=0.001) Figure 3, But no significant correlation was found in both groups between (FT3 and BNP) also (TSH and BNP) Figure1, and Figure 2, respectively.

This result was in agreement with that reported by Christ –Grain and colleagues at 2005 [47], who found that serum NT-proBNP levels were increased in patients with OHyper and there was a significant positive correlation between BNP levels and FT4.

CONCLUSIONS

This study showed that BNP level is influenced by thyroid function. That THs stimulate the secretion of BNP, which in turn BNP has an important role in regulation of the altered hemodynamic changes in OHyper, since OHyper induces elevation in heart rate, blood volume, reduction in SVR and an increase in cardiac out-put. Therefore, OHyper should be considered in any patient presented with mildly elevated BNP level.

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Conflict of interests

The author declares no conflict of interest.

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