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ORGINAL ARTICLE

Value of Brain Natriuretic Peptide in Diagnosis and Control of Hyperthyroid Patients

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Abstract

Background: Brain natriuretic peptide (BNP) is released from the ventricular myocardium as a reaction to volume expansion and pressure overload. Since the thyroid hormones stimulate the release of BNP, it can be used as an indicator of thyroid failure and guiding in thyroid control. This study was THUS designed to assess the value of measuring serum BNP as a marker for diagnosis and follow up of patients with subclinical and overt hyperthyroidism. **Patients and Methods:** This is a prospective cohort study for patients with hyperthyroidism. Patients have been enrolled from Endocrinology Outpatient Clinic at Zagazig University Hospitals in the period from December 2018 to October 2020. **Results:** Patients were divided into two major groups; overt hyperthyroidism (group 1) and subclinical hyperthyroidism (group 2). In all cases BNP level over 100 ng/l. Median for BNP in group (1) 671.89 and the median BNP in group (2) 318.19. We noticed a significant elevation of BNP levels in group (1) than group (2) (p = <0.001), Hyperthyroid patients with major clinical symptoms had showed higher BNP levels (656.9) than those with minor clinical complaint (314 .6) (p =<0.001). Positive correlations between BNP, F.T4 (p= <0.001) and F.T3 (p= <0.001) were documented. But there was no correlation between BNP and TSH or BMI (p= 0.595, p 0.104 respectively). **Conclusions:** BNP levels were significantly elevated in all patients of the study, especially in overt hyperthyroid than subclinical hyperthyroid patients.

Key words: Brain Natriuretic Peptide; Control; hyperthyroid.

INTRODUCTION

Hyperthyroidism is a medical disorder that occurs due to over secretion of thyroid hormones by the thyroid gland to be differentiated from thyrotoxicosis, which is defined as the condition that occurs due to thyroid hormone excess of any cause and so includes hyperthyroidism **[1]**. Subclinical hyperthyroidism is identified by a low or undetectable levels of serum thyroid stimulating hormone (TSH) with free triiodothyronine (F.T3) and free thyroxine (F.T4) levels within laboratory reference ranges **[1]** .BNP is mainly synthesized and released by ventricular myocytes as a reaction to pressure overload or volume expansion of the ventricles .Hence, the concept of application of peptide hormone BNP as a predictor of high volume and pressure load in cardiac patients **[2]**. Previous studies had observed the relation between BNP levels and thyroid hormones. BNP level was found to be 4-fold higher in hyperthyroid patients than euthyroid patients **[3]**. It is postulated that thyroid hormones may stimulate the release of BNP, in addition to the main physiologic process: stimulation via stretching of the atrial myocardial tissue. Prior studies have shown that free T3 hormone directly stimulates the production of BNP from myocardial cells by increasing gene expression **[3]**. Depending on the previous data this study was designed to evaluate the value of measuring serum brain natriuretic peptide as a marker for subclinical hyperthyroidism and documenting the impact of control of hyperthyroidism on BNP level in the serum.

PATIENT AND METHODS

This prospective cohort study was planned to evaluate 48 patients with hyperthyroidism. They

were categorized into two groups, group (1) 24 patients with overt hyperthyroidism and group (2) 24 patients with subclinical hyperthyroidism. All were from18 to 65 years old, both sexes included in the study excluding pregnant and lactating patients. All of them must have low suppressed TSH level. Excluding all patients having heart failure, diastolic dysfunction, acute coronary syndrome, hypertension with left ventricular hypertrophy, valvular heart disease (aortic stenosis, mitral valve regurgitation), atrial fibrillation, acute pulmonary embolism, pulmonary hypertension (primary or secondary), sepsi, chronic obstructive pulmonary disease with corpulmonale or respiratory failure and finally known diabetics. They were recruited from the Endocrinology Outpatient Clinic at Zagazig University Hospitals in the period from December 2018 to October 2020. Clinical and laboratory data were obtained such as age, gender, neck examination, eye examination and routine laboratory investigations. Plus, thyroid function tests, thyroid scan examination, Echo cardiographic evaluation and BNP testing in the serum. After careful evaluation of the patients, some had major clinical symptoms (for example cardiac symptoms like palpitations or even developing heart failure, anxiety and, or thyroid eye disease) and the others had minor clinical symptom like (fine tremors, increased alertness and, or starring look).

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

SAMPLING: Fasting blood samples were obtained by the venipuncture of the large antecubital veins of the studied patients without stasis, after a 12-hour fast. The samples were then centrifuged immediately; the plasma was separated and stored at –80°c. To avoid variation, all samples were studied on the same day and the same kit. TSH, free T3, and free T4 were determined by immunometric assays (Diagnostic Products Corporation, Los Angeles, USA). BNP was measured from the venous whole blood taken into a tube with EDTA.

BNP concentrations were determined with a 2-site sandwich chemiluminescent immunoassay (LotNo: 22161145, reference no: 02816634) on the ADVIA® centaur® platform (Siemens Healthcare Diagnostic, IL, USA). The limit of detection for this assay was 2 ng/L with total imprecision (as CV< 5%) at concentrations of 29 to 1400 ng/L. The ADvIA centaur BNP test measures the physiologically active form of B-type natriuretic peptide, the most clinically relevant form of BNP. BNP kit is an Enzyme – Linked Immunosorbent Assay. This plate has been pre-coated with human BNP antibody. BNP present in the sample was added and blinded to antibodies coated on the wells. And then biotinylated human BNP antibody was added and blinded to BNP in the sample. Then streptavidin-HPR was added and blinded to the biotinylated BNP antibody. After incubation unbound streptavidin –HPR is washed away during a washing step. Then substrate solution was added, and color developed in proportion to the amount of human BNP. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450nm.Optical density (OD) of each well was determined using a microplate reader set to 450nm within 10 minutes after adding stop solution. The standard curve linear regression equation was calculated out. And then, the OD values of the sample were applied on the regression equation. According to standard concentration and the corresponding OD values, calculate the corresponding sample's concentration. Assay range: 5-2000 ng/ml. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

STATISTICAL ANALYSIS

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20 (IBM corp. Released 2011, IBM SPSS statistics for windows, Version 20.0, Armonk, NY: IBM Corp.). Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies. Focusing on the differences in TSH, F.T4 and F.T3 levels between both groups of study. Also documented the difference between BNP levels in both groups. Spearman rank correlation coefficients were used to assess strength and direction of a linear relationship between BNP and other variables in the study. p value that was ≤0.05, considered statistically significant.

RESULTS

Forty-eight patients were included in the study, they were divided into 24 patients with overt hyperthyroidism (group 1) and another 24 patients with subclinical hyperthyroidism (group 2). As shown in Table (1) Median age of overall patients was 41 years ranging from 22 to 65 years old. The female: male ratio was {3: 1}, 36 (75%) of them were

females and 12 (25%) males. The median for BMI was (29.2).

Table (2) shows in group (1) patients the median TSH level was 0.02, median for F.T4 level was 26.09 and F.T3 median level 8.32. In group (2) patients TSH median was 0.04, F.T4 median was 21.0 and F.T3 median was 5.75. We noticed that there was a highly statistically significant variation between the two groups as regard F.T4 (P = <0.001) and also F.T3 (p = <0.001), but no significant difference in TSH (p = 0.223). In Table (3), all population of the study had higher BNP levels over than one hundred (100) ng/l. The median for BNP in group (1) 671.8 and the median BNP in group (2) 318.19. We noticed that there was Statistical significance and variance between the two groups (p =<0.001) in which BNP levels were significantly higher in group (1) overt hyperthyroid group than group (2) subclinical hyperthyroidism.

Table (4) shows that BNP level was significantly elevated in uncontrolled hyperthyroid patients than patients with clinical improvement (p =<0.001). Table (5): as shown in this table BNP levels were significantly higher in older patients (p = 0.003). Also, BNP had highly significant positive correlation with F.T4 (p= <0.001) and FT 3 (p= <0.001). On the other hand, there was no significant correlation between BNP and TSH or BMI (p= 0.595, p 0.104 respectively).

Referring to Figure (1), BNP levels at cutoff ≤350 had an AUC of 0.965with a sensitivity of 81.82% and a specificity of 100%, with highly statistical significance (P= <0.001) as a marker for Clinical improvement and control of thyroid dysfunction. Figure (2) shows that in the overt hyperthyroid group (1) BNP levels at cutoff ≤ 432 there was an AUC of 0.944 with a sensitivity of 83.33% and a specificity of 91.67% with statically significance (P= <0.001) as a marker for diagnosis of hyperthyroidism

Table (1): Clinico-demographic data of the studied population (N= 48)

		Values	
		N	%
Sex (M or F)	Female	36	75.0%
	Male	12	25.0%
Age (years)	Mean ±SD	44±13	
	Median	41 (22-65)	
BMI kg/m^2	Mean ±SD	29.2±2.5	
	Median	29.2 (24.8-33.6)	
Hyperthyroidism	Overt Hyperthyroidism (Group 1)	24	50%
	Subclinical Hyperthyroidism (Group 2)	24	50%

BMI (Body Mass Index)

Table (2): Thyroid profile in both groups (markers for thyroid function: TSH–F. T4– F.T3)

	Group				**Total**		**MW-test**	**P**
	Overt Hyperthyroidism Group (1)		**Subclinical Hyperthyroidism Group (2)**					
	Median	**Range**	**Median**	**Range**	**Median**	**Range**		
TSH mIU/L	0.02	0.01-0.08	0.04	0.01-0.12	0.03	0.01-0.12	-1.2	0.223
F.T 4 ng/dl	26.09	22.00-35.81	21.00	18.00-23.70	23.00	18.00-35.81	-5.4	**0.001
F.T3 pg/ml	8.32	6.90-12.00	5.75	3.60-7.00	7.00	3.60-12.00	-5.8	**<0.001

TSH (thyroid stimulating hormone), F.T4 (free thyroid hormone T4), F.T3 (free thyroid ***p≤0.001 is statistically highly significant, MW-test is a Mann-Witenny test.

Table (3): Comparison of the levels BNP. ng/L in both groups

	Group				Total		MW-test	P
	Overt Hyperthyroidism Group (1)		Subclinical Hyperthyroidism Group (2)					
	Median	Range	Median	Range	Median	Range		
BNP. ng/L	671.89	350-1310	318.19	187.67-640.5	542.78	187.67-1310	-5.3	**<0.001

BNP (Brain Natriuretic Peptide), **p≤0.001 is statistically highly significant, MW-test is a Mann-Witenny test.

Table (4): BNP. ng/L levels in patients who were complaining and were improved.

	Clinical		MW-test	P
	Improved	Symptomatic		
BNP. ng/L	314.6 (187.7-590.9)	656.9 (350.0-1310.0)	-5.4	**<0.001

BNP (Brain Natriuretic Peptide), **p≤0.001 is statistically highly significant, MW-test is a Mann-Witenny test.

Table (5): Correlations between serum BNP (ng/L) level and certain studied parameters in the whole group of study

	BNP (ng/L)	
	r (Correlation coefficient)	Sig.
Age	-0.415	*0.003
TSH mIU/L	-0.079	0.595
F.T 4ng/d	0.680	**<0.001
F.T3 pg/ml	0.690	**<0.001
BMI kg /m^2	0.238	0.104

BNP (B –type natriuretic peptide), TSH (thyroid stimulating hormone), F.T4 (free thyroid hormone T4), F.T3 (free thyroid hormone T3), (BMI) body mass index.

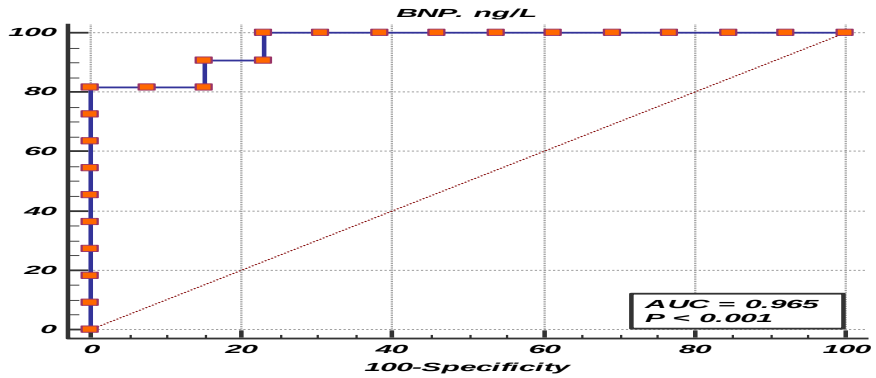

Figure (1) Area under the ROC curve (AUC) of serum BNP (Brain Natriuretic Peptide) as a marker for Clinical improvement and control of thyroid dysfunction.

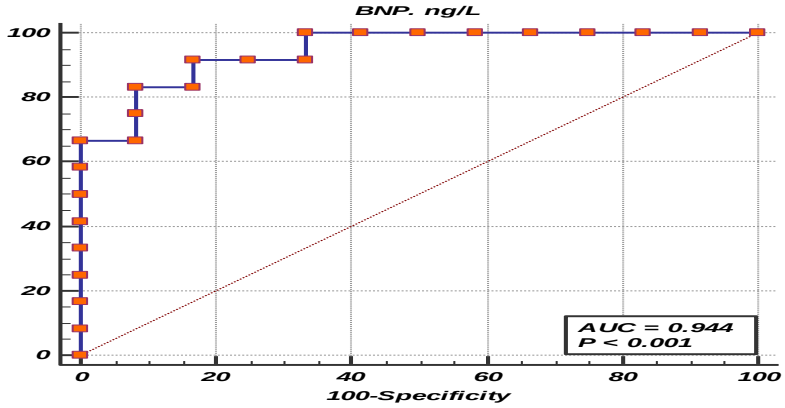

Figure (2) AUC of serum BNP as a diagnostic marker for overt Hyperthyroidism.

DISCUSSIONS

It was noticed that thyroid function status could affect serum BNP levels, which was mostly related to a direct excitatory effect of thyroid hormones on the release of BNP **[4]**. Several published studies observed the levels of BNP in hyperthyroid patients **[5-11]**. some studies showed that there was significant relation between BNP and thyroid functions and other studies did not report any significance. So, at this study we shed light on the value of measuring serum brain natriuretic peptide as a marker for thyroid function status and documenting the impact of control of hyperthyroidism on BNP level in the serum. The current study reported that the BNP levels were elevated in both groups above normal levels, with significant elevation in overt hyperthyroidism than subclinical hyperthyroidism patients. Previous studies reported that hyperthyroid patients had higher plasma levels of BNP and this increase was particularly pronounced in cases of overt hyperthyroidism **[4, 5]**. On the contrary, **Assaad et al. [6]** stated that Serum BNP in the hyperthyroid group was within the reference range in all patients, and there was no significant difference in serum BNP levels between the hyperthyroid and control group without any clarification of these results.

Focusing on the relation between BNP and thyroid hormones, we noticed that there was significant positive relation between BNP and thyroid hormones (F.T3 and F.T4), this comes in agreement with **Arikan et al. [7]** who documented a positive correlation between serum BNP and thyroid hormones. On the contrary, we observed that there was no significant correlation between TSH and BNP levels; this comes in accordance with **Ertugrul et al. [8]** who found that there was no correlation between BNP levels and TSH levels.

When studying BNP in relation to BMI, there was no significant correlation. Also, **Arikan et al.'s [7]** study, could not find any correlations between BNP levels and BMI. On the contrary, Wang study documented that there was inverse relationship between obesity and BNP levels **[9]**. Another study, Taylor study had also found that obese patients have reduced concentrations of BNP compared to non-obese patients **[10]**.

When studying BNP in relation to dysthyroid clinical state, we observed that patients with major clinical symptoms had showed higher BNP levels than those with minor complaints. This comes in accordance with the studies of **Ertugrul et al. [8] and Schultz et al. [11]**, who observed significant decrease in BNP levels, after euthyroidism was achieved. This finding supports the importance of BNP to guide therapy in subclinical hyperthyroid patients.

The current study had documented a strong cross linkage between BNP and thyroid eye disease. There were statistically significantly higher BNP levels in patients with abnormal eye presentation (thyroid eye disease) (p= 0.03). So, BNP could be used as predictor of risk of developing thyroid eye disease in the future.

One of the limitations in our study is that our study aimed to estimate any significant association between thyroid dysfunction and BNP, but we did not include in the study control group or hypothyroid group for more inclusive comparison. Another limitation of this study is that we did not observe patients before and after treatment with antithyroid medications. So, we recommend that our results should be validated in larger cohorts of patients in the future of different geographic areas and different etiologies to support the correlation between BNP and hyperthyroidism. Moreover, if it can be applied as a marker for subclinical hyperthyroidism instead of TSH who might be suppressed for longer durations. The cutoff value of BNP needs to be adequately determined in further studies. Testing for thyroid function is essential before accepting BNP as marker for heart failure.

CONCLUSIONS

In view of the current study, BNP levels were markedly elevated in hyperthyroid patients, more prominently in overt hyperthyroid than subclinical hyperthyroid group. Also, the Levels of BNP were higher in patients with uncontrolled hyperthyroid state and still suffering than patients with minor clinical complaint. BNP can be used as a guide for therapy specifically for deintensification of therapy.

Conflict of interest: The authors declare no conflict of interest.

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REFERENCES

[1] Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract. 2011 May-Jun;17(3):456–520. doi: 10.4158/ep.17.3.456.

[2] Kerkelä R, Ulvila J, Magga J. Natriuretic Peptides in the Regulation of Cardiovascular Physiology and Metabolic Events. J Am. Heart

Assoc. 2015 Oct; 4(10): e002423. doi: 10.1161/JAHA.115.002423.

[3] Chiaki K., Ryo N, Hiroki K., Tomohiro K., Kosuke Y., Midori K., et al. Heart Failure with Hyperthyroidism Demonstrating Discrepancy between the Clinical Course and B-type Natriuretic Peptide Levels. Intern Med. 2018 Jun 15; 57(12): 1747–1749. Published online 2018 Feb 9. doi: 10.2169/internalmedicine.0118.

[4] Ertugrul DT, Gursoy A, Sahin M, Unal AD, Pamuk B, Berberoglu Z, et al. Evaluation of brain natriuretic peptide levels in hyperthyroidism and hypothyroidism. J Natl Med Assoc. 2008 Apr;100(4):401–5. doi: 10.1016/s0027-9684(15)31272-4. PMID: 184814.

[5] Pakuła D, Marek B, Kajdaniuk D, Krysiak R, Kos-Kudła B, Pakuła P, et al. Plasma levels of NT-pro-brain natriuretic peptide in patients with overt and subclinical hyperthyroidism and hypothyroidism. Endokrynol Pol. 2011;62(6):523–8. PMID: 22144219.

[6] Assaad SN, Ghitany MK, Marzouk SA, Lotfy MI, Swidan AK, El-Zawawy HT. Study of copeptin and brain natriuretic peptide in patients with thyroid dysfunction: relation to cardiovascular performance. Egypt J Obes Diabetes Endocrinol 2015;1: 6571.

[7] Arikan S, Tuzcu A, Gokalp D, Bahceci M, Danis R. Hyperthyroidism may affect serum N-terminal pro-B-type natriuretic peptide levels independently of cardiac dysfunction. - Clin. Endocrinol. (Oxf). 2007; 67 (2); 202.

[8] Ertugrul DT, Yavuz B, Ata N, Yalcin AA, Kucukazman M, Algul B, Dal K, et al. Decreasing brain natriuretic peptide levels after treatment for hyperthyroidism. Endocr. J. - January 1, 2009; 56 (9); 1043–8.

[9] Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW. Impact of obesity on plasma natriuretic peptide levels. Circulation. 2004 Feb 10; 109(5):594–600.

[10] Taylor JA, Christenson RH, Rao K, Jorge M, Gottlieb SS. B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide are depressed in obesity despite higher left ventricular end diastolic pressures. Am Heart J. 2006 Dec;152(6):1071–6. doi: 10.1016/j.ahj.2006.07.010.

[11] Schultz M, Kistorp C, Raymond I, Dimsits J, Tuxen C, Hildebrandt P, et al. Cardiovascular events in thyroid disease: a population based, prospective study. Horm Metab Res. 2011; 43:653–659.

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