# High brain natriuretic peptide and its related diastolic dysfunction respond to anti-thyroid drugs in patients with overt hyperthyroidism.

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**Abstract: Background:** Brain natriuretic peptide (BNP) is influenced by hyperthyroidism. The objective of this study was to study the relation between the BNP levels and echocardiographic parameters in hyperthyroid patients and the effect of anti-thyroid therapy. **Methods**: this is a cohort study, that recruited a 100 drug-naïve patients with overt hyperthyroidism attending King Fahd Hospital in Madina during the period from October 2008 to December 2010. None of the patients showed clinical or echo-cardiographic evidence of heart failure. Plasma BNP levels and trans-thoracic echocardiography were assessed initially and then six weeks after anti-thyroid drugs. **Results**: basal BNP level was elevated (49.57 ± 5.03 pg/mL), with a significant drop (38.56 ± 5.19 pg/mL, $p$ = 0.000) after anti thyroid therapy. The difference in BNP level correlated positively with the differences in both the clinical score (r = 0.729, $p$ = 0.000) and the biochemical thyroid function (FT4: r = 0.312, $p$ = 0.004; and FT3: r = 0.536, $p$ = 0.00). It also correlated positively with the differences in the diameter of the left atrium (r = 0.366, $p$ = 0.006); negatively with the difference in fractional shortening (r = –0.381, $p$ = 0.004), and early diastolic velocity (r = –0.371, $p$ = 0.016). Conclusion: results demonstrate that BNP increases mildly in patients with overt hyperthyroidism and it is associated with subclinical diastolic dysfunction. Both serum thyroid hormones and cardiovascular dysfunction could contribute to the increase in BNP levels. High BNP and diastolic dysfunction responded to 6 weeks of anti-thyroid therapy.

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## 1. Introduction:

Hyperthyroidism stresses the cardiovascular system; it reduces its functional capacity and can precipitate heart failure. The hemodynamic derangement is mediated through combined effects of excess thyroid hormone on the heart and on the peripheral vascular system at both the genomic and non-genomic molecular pathways (1). The resultant cardiac dysfunction is associated with normal or marginally increased left ventricular end-diastolic diameter and normal or marginally decreased left ventricular end-systolic diameter with increased ejection fraction (2). These cardiac changes are usually subclinical and may be under –estimated during echocardiography (3). Brain natriuretic peptide (BNP) level is a cardiac biomarker of left ventricular dysfunction and de-compensated heart failure (4). Both animal and human studies indicated that the BNP inhibits synthesis of thyroid hormone whereas thyroid hormone enhances BNP production and genetic expression (6-8). Studies show that BNP also mediates thyroid hormone related cardiovascular effects (9). On the other hand, excess thyroid hormone that induces ventricular stretch and pressure overload could mediate BNP release in hyperthyroid patients (10). Previous studies found that patients with hyperthyroidism had higher plasma BNP level, which may result in subclinical cardiac dysfunction (11-14). Others found that the cardiac dysfunction is reversible after therapy of hyperthyroidism (15-17). However, there are few data regarding the relation between subclinical cardiac dysfunction in overt hyperthyroid patients and high serum BNP level. One study published in 2007 found that the elevated BNP level is independent of cardiac dysfunction (18). To further assess the relationship between BNP levels and the subclinical cardiac dysfunction in patients with hyperthyroidism, plasma BNP levels and echo-cardiographic parameters were measured simultaneously in overt hyperthyroid patients at diagnosis and 6 weeks after the initiation of anti-thyroid therapy.

## 2. Methods:

This cohort study was approved by the local ethical committee of the Deanship of Scientific Research at Taibah University and was conducted in accordance with the Helsinki Declaration on human

experimentation. Written informed consents were obtained from all participants. The study was carried out at the outpatient department of King Fahd hospital in Madina in the period from October 2008 to December 2010. The study population consisted of 100 consecutive newly diagnosed drug-naïve overt endogenous hyperthyroid Saudi patients below the age of 65. Diagnosis of overt hyperthyroidism was based on the level of thyrotropin TSH (< 0.1 mU/L), free thyroxine (FT4) > 14.1 pmol/L and/or free triiodothyronine (FT3) > 7.1 pmol/L. Patients with symptoms or signs of heart failure, artial fibrillation, known with cardiac illness, or with echocardiographic evidence of systolic heart failure (ejection fraction, EF < 40%) were excluded from the study. Patients with subacute thyroiditis or exogenous causes of hyperthyroidism were also excluded. Exclusion criteria also included occurrence of diabetes, hypertension, pregnancy or lactation; hepatic or renal dysfunction, significant neurological or psychological diseases, inflammatory bowel diseases, severe anemia (hemoglobin < 8 gm/dL), and evidence of connective tissue disease.

Patients who had used any medications, such as antihypertensives including angiotensin-converting enzyme inhibitors, beta blockers, diuretics, amiodarone, digoxin, oral contraceptives, antidepressants, anti-serotoninergics, oral corticosteroids, anti-folates, anti-convulsant agents or lipid-lowering agents, within the previous six months, which might affect the study parameters, were also excluded from the study.

All patients underwent an initial screening assessment that included a detailed medical history and complete physical examination. The clinical score was estimated according to Crook's therapeutic index of hyperthyroidism (a measure of the severity of the clinical disease severity) (19).

Treatment for hyperthyroidism was chosen according to the medical guidelines of the American Association of Clinical Endocrinologists for the evaluation and treatment of hyperthyroidism (20). Only anti-thyroid medication(s) were used; other modalities of treatment, such as administration of radioactive iodine and surgery, were not considered during the study period. All patients were followed up after six weeks with no drop out. Levels of FT3, FT4, TSH, and BNP were measured before and after six weeks of treatment.

After 12 hours fast, blood samples were obtained by venipuncture of the large antecubital vein of the studied patients without stasis. The samples were then centrifuged immediately; the plasma was separated and stored at –80 °C. To avoid variations, all the samples were studied on the same day using the same kit. Serum levels of; TSH, free T3, and free T4 were determined by immunometric assays (Diagnostic Products Corporation, Los Angeles, USA). Venous whole blood was taken into a tube that contains ethylenediamine-tetraacetic acid, and the BNP concentrations were measured using a commercially available enzyme-linked immunosorbent assay kit (Phonex Pharmaceuticals, Inc., Europe, GMBH) the manufacturer's instructions were followed. The limit of detection for BNP in plasma as stated by the manufacturers was 1–150 pg/mL.

Standard transthoracic echocardiographic examination was carried out on all patients before the beginning and after six weeks of treatment using 2.5–3.5 MHz transducers at the echocardiographic department. All the echo studies were interpreted by experienced echocardiologists, who were not informed about the patients' clinical presentation, thyroid function status, or BNP results. The following parameters were measured: (1) Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, in cm; (2) Left atrial (LA) and Aortic (AO) diameters (in cm) and the LA/AO ratio; (3) Interventricular septal diameter (IVSD) and left ventricular posterior wall diameter (LVPWD), in cm; (4) Fractional shortening (FS, %); and (5) EF (%). Measurement of transmitral flow velocity indexes (the cornerstone of LV diastolic function evaluation) were obtained using pulsed-wave Doppler in an apical four-chamber view, and measurements were made utilizing the software of the ultrasound equipment. The following indexes were measured from the mitral valve diastolic waveform: peak early (E) and atrial (A) flow velocities (m/s), and the E/A ratio during LV diastolic filling.

**Statistical Methods:**

The sample size required was calculated according to the following formula:

$n = t^2 \times p(1-p)/m^2$ (n= required sample size, t = confidence level at 95% (standard value of 1.96), *p* = estimated prevalence of hyperthyroidism (1.3%), m = margin of error at 5% (standard value of 0.05)). Calculation was performed taking into consideration the design effect, contingency such as non-response or recording error. The sample size required was 79 subjects which increased to 100 to count for drop out. All the study data were analyzed using the SPSS 18.0 software for Windows (PASW statistics 18). Descriptive statistics were used to estimate the frequencies for the categorical variables; and the mean (± SD) values for continuous variables. The paired Student's T-test was used for comparison of the pre- and post-treatment data. Computing variables were used to calculate the differences in the variables after six weeks of treatment. The Pearson analysis was used to identify correlations between the

differences in the BNP levels and the differences in other parameters. For all statistics, a two-sided p-value < 0.05 was considered statistically significant.

**3. Results**

Among the patients, 16 were males and 84 were females, aged 36.09 ± 12.65 years. Of these, 53 cases had Graves' disease (53%) and 47 had toxic nodular goiter (47%). Patients' symptoms mainly included; nervousness, irritability, heat intolerance, excessive sweating (72.7%), weight loss (50%) with increased appetite, and frequent bowel movements (22%). Cardiac symptoms were mainly palpitation (62%). In patients with Graves' disease, 18 patients (18%) showed eye symptoms. None of the patients had apathetic thyrotoxicosis or developed thyrotoxic crisis during the period of the study. Physical examination of almost all the patients showed anxiety, restlessness and fine tremors. The skin of all patients was warm and moist, but none had developed Plummer's nails. Eyelid retraction and lid lag were detected in 70% of the studied cases.

The Cardiovascular findings included; tachycardia and apical systolic murmur. In patients with Graves' disease, the thyroid gland was diffusely enlarged, but no bruit or thrill could be detected in any of the cases. Infiltrative ophthalmopathy, with variable degrees of proptosis and periorbital swelling, was detected in 12 patients (12%) with Graves' disease but none had ophthalmoplegia and none of the patients developed pretibial myxedema. In patients with toxic nodular goiter, multiple nodules were detected by either clinical palpation or ultrasonography.

After six weeks of follow-up under treatment, 16 cases were missed (84% response rate), 15% had persistent palpitation, but none had shortness of breath or chest pain. Biochemically persistent hyperthyroidism was detected in 38 patients (38%), with a good response in 46 patients (46%), that had normal T4 and T3 levels (20 patients became completely euthyroid, and 26 had normal free T4 and T3 with suppressed TSH levels).

Table 1 shows the clinical results and BNP levels pre- and post-treatment in 100 patients with overt hyperthyroidism. The clinical score decreased significantly with treatment (from 24.37 ± 4.2 to 14.70 ± 4.61, $p = 0.00$), associated with a significant increase in TSH (from 0.013 ± 0.01 to 1.01 ± 1.93 mU/L, $p = 0.00$), significant decreases in FT4 (from 28.90 ± 13.00 to 21.74 ± 26.81 pmol/L, $p = 0.023$), and FT3 (from 10.88 ± 6.18 to 7.45 ± 5.61 pmol/L) levels. Initially, the mean BNP level was elevated (49.57 ± 5.03 pg/mL), with a significant drop (38.56 ± 5.19 pg/mL, $p = 0.00$) after therapy. In Table 2, the echocardiography results show that the only detected abnormality was reversed mean E/A ratio (1.29 ± 0.38). There were significant changes involving decreases in LVSD (from 0.93 ± 0.09 to 0.89 ± 0.11 cm, $p = 0.006$), LA (3.34 ± 0.38 to 3.16 ± 0.34 cm, $p = 0.00$), and atrial velocity "A" (from 0.71 ± 0.18 to 0.66 ± 0.17 m/s, $p = 0.039$), with associated increases in early diastolic velocity "E" (from 0.85 ± 0.12 to 0.91 ± 0.18 m/s, $p = 0.005$) and of the E/A ratio (1.29 ± 0.38 to 1.46 ± 0.40, $p = 0.014$).

Results found a significant correlation between the changes in BNP level after therapy and the changes in the clinical score ($r = 0.729$, $p = 0.000$, fig. 1) and changes in thyroid function (FT4: $r = 0.312$, $p = 0.004$; and FT3: $r = 0.536$, $p = 0.000$; figs. and 3 respectively). However, the BNP level was not correlated with TSH ($r = –0.07$, $p = 0.52$). Changes in BNP levels after treatment also had positive correlations with changes in the diameter of the left atrium ($r = 0.366$, $p = 0.006$, fig. 4) and negative correlations with FS ($r = –0.381$, $p = 0.004$, fig. 5), and early diastolic velocity "E" ($r = –0.371$, $p = 0.016$; fig. 6).

Table 1: The clinical scores, BNP levels, pre- and post-treatment in patients with overt hyperthyroidism.

| Variables | Mean ± SD | *p*-value |
|---|---|---|
| Clinical Score | ❖24.34 ± 4.20 | 0.000 |
| | ◆14.70 ± 4.61 | |
| TSH, mU/L | ❖0.013 ± 0.009 | 0.000 |
| | ◆1.01 ± 1.93 | |
| $FT_4$, pmol/L | ❖28.90 ± 13.00 | 0.023 |
| | ◆21.74 ± 26.81 | |
| $FT_3$, pmol/L | ❖10.88 ± 6.18 | 0.000 |
| | ◆7.45 ± 5.61 | |
| BNP, pg/mL | ❖49.57 ± 5.03 | 0.000 |
| | ◆38.56 ± 5.19 | |

pre- (❖) and post (◆) treatment

Table 2: The echocardiographic parameters pre- and post-treatment in patients with overt hyperthyroidism.

| Variables | Mean ± SD | *p*-value | Variables | Mean ± SD | *p*-value |
|---|---|---|---|---|---|
| IVSD, cm | ❖0.93 ± 0.09 | 0.006 | LA/AO ratio | ❖1.10 ± 0.16 | 0.003 |
| | ◆0.89 ± 0.11 | | | ◆1.03 ± 0.12 | |
| LVEDD, cm | ❖ 4.90 ± 0.51 | 0.460 | FS, % | ❖39.20 ± 5.16 | 0.220 |
| | ◆4.86 ± 0.33 | | | ◆40.10 ± 4.49 | |
| LVESD, cm | ❖ 2.99 ± 0.48 | 0.173 | EF, % | ❖68.63 ± 6.52 | 0.926 |
| | ◆2.91 ± 0.40 | | | ◆68.72 ± 8.09 | |
| PW, cm | ❖.87 ± 0.16 | 0.233 | E, m/s | ❖0.85 ± 0.12 | 0.005 |
| | ◆.84 ± 0.07 | | | ◆0.91 ± 0.18 | |
| AO, cm | ❖3.08 ± 0.43 | 0.663 | A, m/s | ❖0.71 ± 0.18 | 0.039 |
| | ◆3.06 ± 0.37 | | | ◆0.66 ± 0.17 | |
| LA, cm | ❖3.34 ± 0.38 | 0.000 | E/A Ratio | ❖1.29 ± 0.38 | 0.014 |
| | ◆3.16 ± 0.34 | | | ◆1.46 ± 0.40 | |

pre- (❖) and post (◆) treatment

IVSD: interventricular septal diameter, LVEDD: LV end-diastolic didiameter, LVESD: LV end-systolic diameter, PW: posterior wall diameter, AO: aortic root diameter, LA: left atrium diameter, FS: fractional shortening, EF: ejection fraction, A: atrial velocity, E: early diastolic velocitY

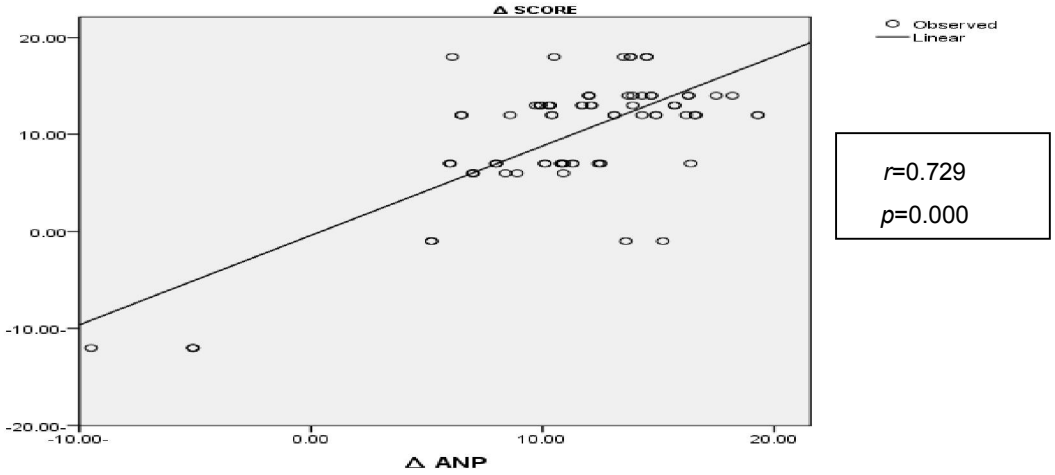


Figure 1: Significant positive correlation between the changes in BNP level and the changes in the clinical score after therapy

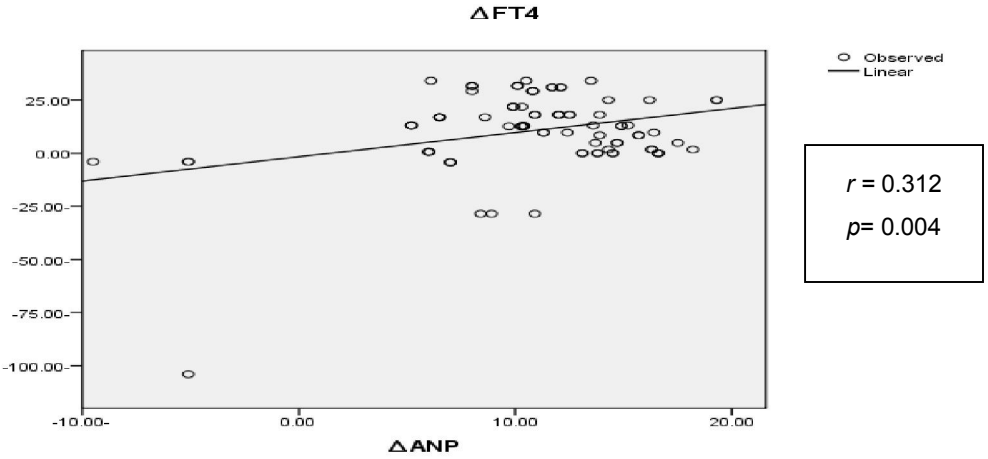


Figure 2: Significant correlation between the changes in BNP level and thechanges in the FT4 after therapy

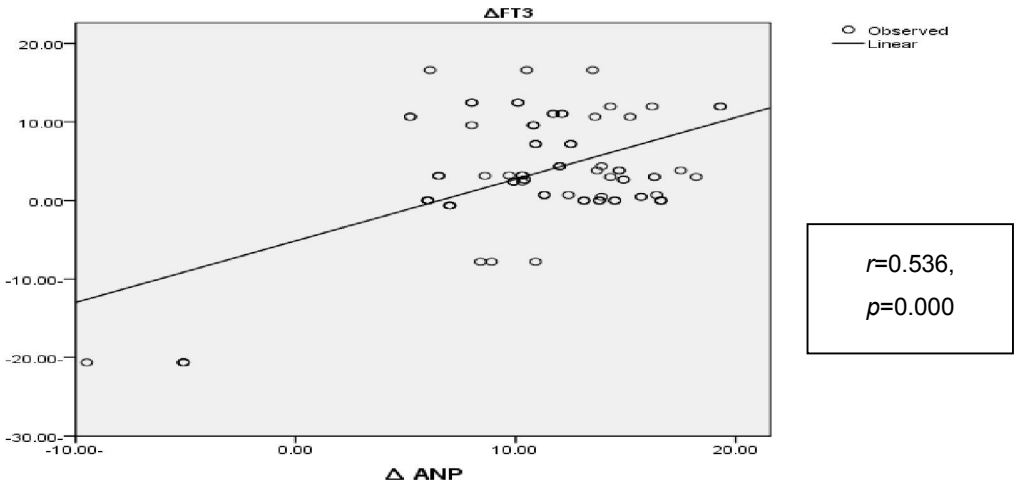


Figure 3: Significant positive correlation between the changes in BNP level and the changes in the FT3 after therapy

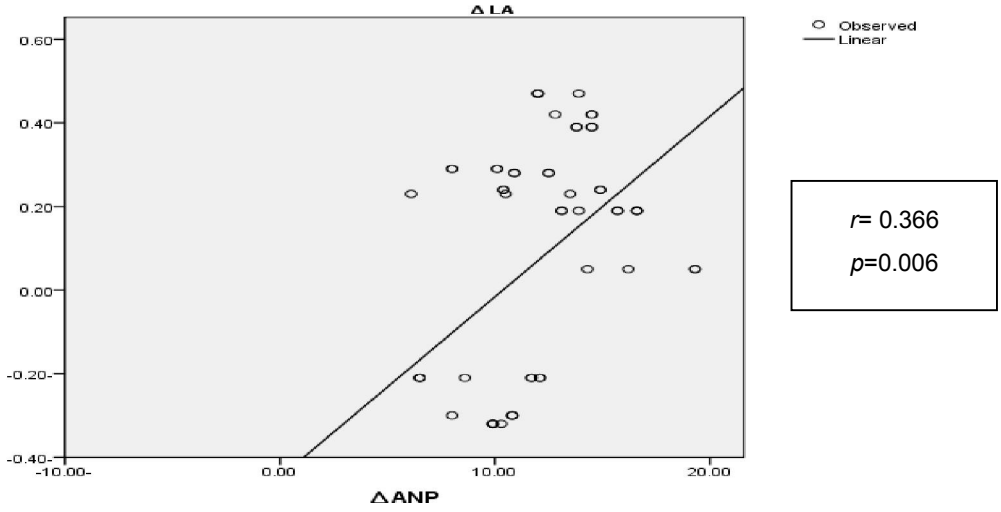


Figure 4: Significant negative correlation between the changes in BNP level and the changes in the LA (left atrium) after therapy

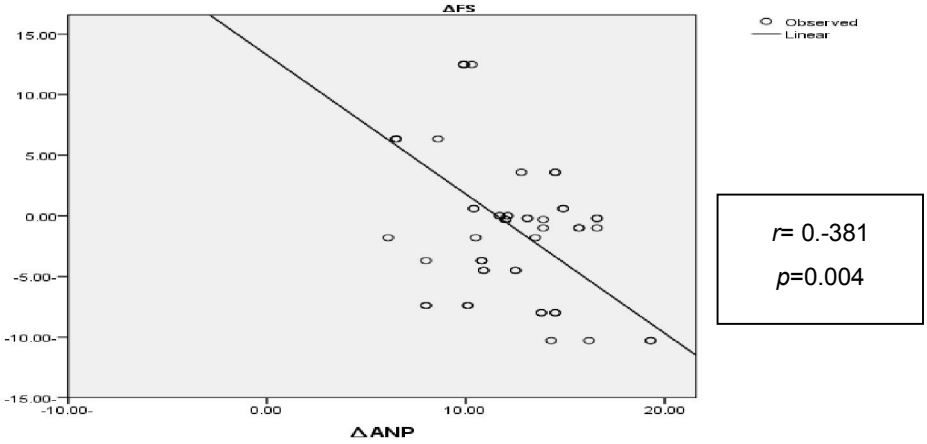


Figure 5: Significant negative correlation between the changes in BNP level and the changes in the FS (fractional shortening) after therapy

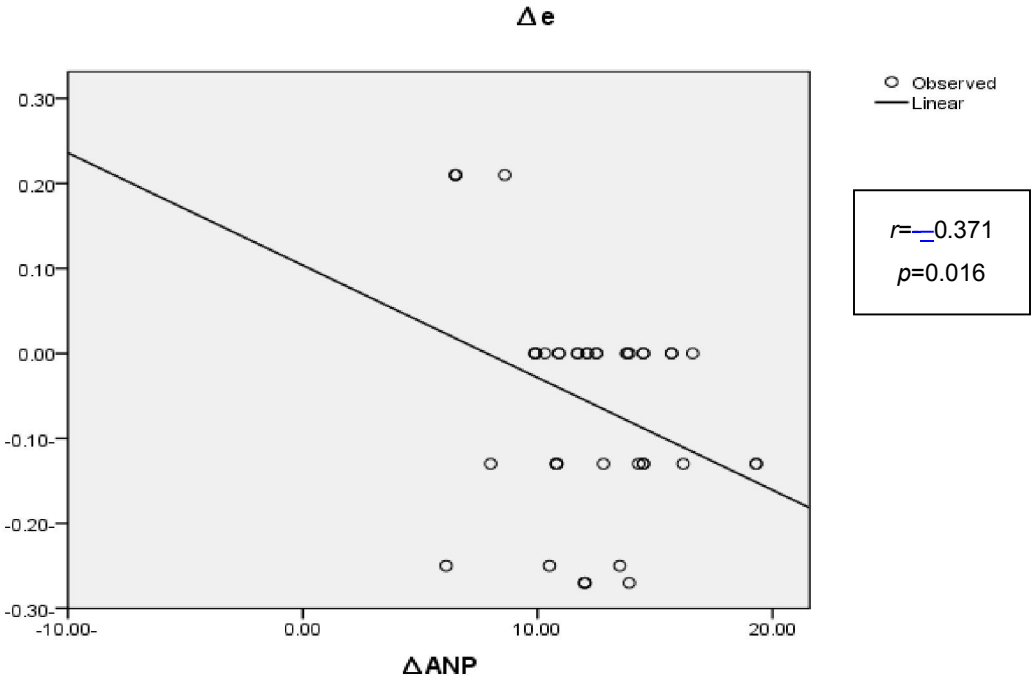


Figure 6: Significant negative correlation between the changes in BNP level and the changes in the e (early diastolic velocity) after therapy

**4. Discussion**

This study showed a mild increase in BNP level in patients with overt hyperthyroidism associated impaired Doppler parameters of diastolic function. After 6 weeks of anti-thyroid therapy, there was a fall of BNP levels in association with improvement in the clinical, biochemical, diastolic function as well as fractional shortening. These cardiac changes induced by excess thyroid hormone may explain the elevation of BNP levels detected in those patients.

Studies show that T3 and T4 stimulated the release of BNP from both cultured atrial and ventricular myocytes in a dose-dependent manner (21) and triiodothyronine also increases the transcription of the BNP gene and amplifies endothelin-dependent BNP gene transcription in rat ventricles (22).

The reason behind BNP elevation in hyperthyroidism is still not clear. However, the atrial stretch that result from the hemodynamic changes and the volume expansion in patients with hyperthyroidism appears to be the main responsible mechanism. This was in agreement with our results and evident by the BNP positive correlations and by the improvement that was documented after treatment in both the left atrial abnormality and the early diastolic atrial velocity "E". The diagnosis of diastolic dysfunction and heart failure is not easy. BNP has recently been shown to reliably detect the presence of diastolic dysfunction if performed with echocardiography (23, 24).

Systolic dysfunction expected to be seen in hyperthyroid patients is usually un-determined by conventional echocardiography (1, 3) as seen in this study. However, our finding of the negative correlations between BNP changes and the improvement in fractional shortening with treatment could be interpreted as an improvement in systolic dysfunction after antithyroid treatment, irrespective of the absolute basal echocardiographic readings. Again this could reflect the importance of BNP estimation in addition to the echo-cardiograpic parameters in assessing both systolic and diastolic cardiac changes especially in hyperthyroidism.

In agreement with our study, other researchers found a significant elevation of BNP levels in patients with thyrotoxicosis (13-18). Biondi *et al*. demonstrated an increase of septal wall thickness, and impaired Doppler parameters of diastolic function (25). Smit *et al*. stated that diastolic dysfunction was impaired in exogenous subclinical hyperthyroidism that was induced by levothyroxine treatment in 25 differentiated thyroid carcinoma patients (26). While, Wei *et al*. (13) detected high BNP levels, especially in the hyperthyroid patients with left ventricular dysfunction. The positive

correlations between BNP and thyroid hormones detected in our study as well as in others (15, 18) are not supported by Wei *et al*. (13) who found a correlation between atrial diameter and BNP only.

In our study, the significant decrease in BNP levels after therapy was positively correlated with the decreases in T3 and T4, but not with the TSH, levels. The absence of correlation with TSH in the follow-up period could be explained by the fact that TSH level may not be a good indicator of thyroid function because its levels takes more time to increase (27). Studies in both overt and subclinical hyperthyroidism that evaluated the effect of anti-thyroid treatment on high BNP level had more or less similar findings (15, 28–30).

The strength of this study is its cohort's design, allowing studying the effect of therapy on all parameters. The major limitation of our study was the occurrence of confounders that affect the level of plasma BNP and not excluded in this study as genetic influences (31), abnormalities in cardiac performance (32), female gender (33) and high body mass index (34).

In conclusion; The BNP mildly increases in patients with overt hyperthyroidism and is associated with diastolic dysfunction. Because of the significant correlation between the fall in BNP with therapy and the improvement of thyroid hormones and systolic as well as diastolic dysfunction, it could be concluded that both serum thyroid hormones and cardiovascular dysfunction contribute to the increase of serum BNP levels in hyperthyroid states (35). The use of simple blood tests, such as estimation of BNP level, to screen patients with underlying cardiac dysfunction is an attractive strategy in patients at risk of heart failure secondary to hyperthyroidism. Nevertheless, larger prospective studies must be carried out to define appropriate cut-off ranges, screening time intervals, and potential benefits of intervention based on elevated plasma levels of natriuretic peptide before a screening strategy can be effectively implemented.

**Declaration of interest:**

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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