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N TERMINAL PRO BNP AND SERUM SOLUBLE ST2 IN THYROID DISORDERS

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Abstract
Background: There are only a few studies investigating the influence of thyroid hormones on BNP and ST2 levels, these studies have conflicting results. We have estimated serum Soluble ST2 and B -type natriuretic peptides in thyroid disorders, and explored the relationship of thyroid stimulating hormone in newly diagnosed hypo and hyper thyroid individuals.
Methodology: This is cross sectional study was carried out in newly diagnosed hypo-thyroid and hyper-thyroid females with age matched controls. Each group consisted of 45 individuals. They were controls, Newly diagnosed hypo-thyroid and hyper-thyroid subjects. fT3, fT4 and TSH were analyzed using commercially available chemiluminescence assay kits, NT pro BNP, serum ST2 were assessed by commercially available ELISA kits.
Results: Significant difference was seen in NT pro BNP ($p < 0.000$) and ST2 ($p < 0.001$) between controls, hypo-thyroid subjects and hyper-thyroid subjects. Further within group observations showed significantly higher NT pro BNP ($p <0.05$) and low ST2 ($p < 0.05$) in hyperthyroid subjects when compared to hypothyroid subjects. The higher thyroid stimulating hormone levels were positively correlated with, NT pro BNP ($r = 0.537$; $p < 0.000$) and ST2 ($r = 0.42$; $p < 0.000$).
Conclusion: This increased N T Pro BNP levels in both newly diagnosed hypo and hyperthyroidism indicates that there will be a left ventricular dysfunction or they may be at risk of development of acute coronary syndromes, and the ST2 is an indicator of indicator of increased risk of future cardiovascular mortality.
Keywords: Hypothyroidism, Hyperthyroidism, N terminal Pro BNP, Soluble ST2.

Introduction: Recent reports have documented a gene ST2 (suppression of tumorigenicity) and its connected protein which especially promoted in precisely induced in mechanically overloaded cardiac myocytes. This proposed that that the protein can be over-expressed in remaining myocardium that has gone through higher levels of stress (1). ST2 is engaged in function and dysfunction of cardiovascular system. Activity of ST2 on heart muscle is perplexing and not completely comprehended and it is firmly identified with IL-33 method of activity. IL-33 could be restricted at the same time onto nuclear euchromatin and membrane-bound cytoplasmic vesicles. Kakkaret al. (1) reported that the mechanical stretch of living cells could enhance the release of IL-33 from the cytoplasmatic vesicles. Such an exocytosis was not identified to a potential stretch-initiated necrosis: the cells viability was demonstrated after the periods of biaxial stretch. accordingly, the cell stretch can lead to release of IL-33.

The structure of atrial natriuretic peptide (ANP) was first found in 1984. In following years, an atom, the natriuretic and diuretic impacts of which looked like those of ANP, was confined from a pig brain. In spite of the fact that this peptide is alluded to as the brain natriuretic peptide (BNP), it is really created in the ventricular myocardium. BNP isn't a prestored particle, however on the off chance that appropriate improvements exist it very well may be delivered quickly through mRNA amalgamation. The stimulus for discharge of BNP by the ventricles of the heart is fundamentally over stretching of cardia myocyte as opposed to the transmural pressure load.

BNP will be sybtesized both in an inactive N-terminal part with 76 amino acids (NT-pro BNP) and an active-hormone with 32 amino acids (BNP). The impacts of ANP and BNP are fundamentally the same. In renal system, the expanded glomerular filtration causes the restraints reabsorbtion of sodium and along these lines natriuresis and diuresis (2). Estimation of BNP levels have as of late been presented as a noninvasive, minimal risk test that estimates circling levels of BNP, which are raised in people with both suggestive and asymptomatic cardiac failure. This test is being utilized to identify preclinical coronary illness or to affirm the cardiovascular etiology in patients with symptoms. It not just empowers the early recognizable proof of patients with early cardiac failure yet in addition gives prognostic data dependent on the size of the expansion (3).

Hyperthyroidism leads to increased metabolism linked with higher sympathetic activity. Hormones of thyroid gland as facilitates catecholamine functions. However, hyperthyroidism is portrayed by both increased as well as decreased modulation parasympathetic activity on cardiovascular system (4),

The impacts of hyper-thyroidism on cardiovascular system are changes in haemodyamics like reduced resistance of systemic circulation, higher cardiac output, pulse, blood volume, circulatory strain and hindered cardiovascular contractility. These progressions bring about ventricular stretch & pressure over-load, which leads to increased BNP levels in this condition. 0 Late consideration has been attracted to the connection of BNP and hyper-thyroidism. Reports propose that plasma BNP and NT-proBNP

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levels are increased in hyper-thyroidism. This condition is expansion is mostly because of hyper-thyroidism-induced dysfunction of left ventricle. Likewise, hormones of the thyroid may up-regulate BNP discharge from myocytes of both atria and ventricules (5).

Hypo-thyroidism influences somewhere in the range of 4% and 10% population. and the sub-clinical hypo-thyroidism prevalence is accounted as as high as 10% in different studies (6), (7). Hypo-thyroidism is analyzed when lower level of thyroid hormones bring about raised degrees of thyroid stimulating hormone (TSH), while sub-clinical hypo-thyroidism is declared when TSH levels are raised over the maximum furthest reaches of the reference ranges with typical level of hormones of thyroid gland. Hypo-thyroidism produces significant cardio-vascular impacts.

There are only a few studies investigating the influence of thyroid hormones on BNP levels, ST2 levels and these studies have conflicting results.

Therefore, in this study, we have estimated serum Soluble ST2 and B -type natriuretic peptides in thyroid disorders, and explored the relationship of thyroid stimulating hormone with Serum Soluble ST2 Receptor, B type natriuretic peptides and in newly diagnosed hypo and hyper thyroid individuals.

Materials and methods: This is cross sectional study was carried out in newly diagnosed hypo-thyroid and hyper-thyroid females with age matched controls. After getting clearance from institute ethics committee, written informed consent was obtained from all participants. All experiments were performed at research laboratory in the Department of Physiology and Biochemistry, Santhosh Medical College and Rohilkhand medical college and hospital Bareilly. Hypo and hyper thyroid subjects were recruited from Medicine and Endocrinology outpatient departments. Controls were age matched students and residents. They were divided into three groups. Each group consisted of 45 individuals. Group 1: controls, Group 2: Newly diagnosed Hypo-thyroid subjects, Group: Newly Diagnosed Hyper-thyroid subjects

Inclusion criteria: Age: 18 – 35 years, In hypothyroid group, female patients newly diagnosed as primary hypothyroidism, before initiation of the treatment were included. Likewise, newly diagnosed female patients with primary hyperthyroidism, before initiation of the treatment wias taken in hyperthyroid group. For control group, subjects with age matched apparently healthy individuals were recruited.

Exclusion criteria: Patients, who were already on treatment for thyroid disorders, known cases of diabetes mellitus, hypertension, heart diseases, autonomic failure or endocrine disorders and those were on any chronic medications were excluded from the study.

Baseline parameters like height, weight body mass index were recorded before blood collection. Blood samples were collected after 10 hours of fasting. 5ml of blood was collected and allowed to clot. Serum was separated and stored in refrigerator to estimate the fT3, fT4 and TSH were analyzed using commercially available chemilluminesence assay kits (Maglumi, UK, Gentaur, Belgium), NT pro BNP (Ray biotech, USA), serum ST2 (Phoenix pharmaceuticals INC, USA) was assessed by commercially available ELISA kits and lipid profile was carried out by enzymatic method. All assays were carried out as per kit manuals,

Results: The baseline and anthropometric parameters of controls, hypothyroid and hyperthyroid subjects were depicted in Table 1. There was no significant difference in age, height between the groups. Weight ($p<0.000$), Body mass index ($p<0.000$), heart rate ($p<0.000$), systolic blood pressure ($p<0.000$), diastolic blood pressure ($p<0.000$), were significantly different between the groups.

Further, body weight of hypothyroid subjects ($p < 0.05$) was significantly high and significantly low in hyperthyroid subjects ($p < 0.05$). Body mass index ($p < 0.05$) was high in hypothyroid subjects and slightly high in hyperthyroid subjects. Heart rate was significantly low in ($p < 0.05$) hypothyroid subjects and high in hyperthyroid subjects ($p < 0.05$) when compared to controls. Further, within groups analysis showed the significantly higher heart rate was seen in hyperthyroid subjects ($p < 0.05$) when compared to hypothyroid subjects.

Systolic and diastolic blood pressure were significantly high in ($p < 0.05$) hypothyroid subjects and high in hyperthyroid subjects ($p < 0.05$) when compared to controls. Further, within groups analysis showed the significantly higher Systolic and diastolic blood pressure in hyperthyroid subjects ($p < 0.05$) when compared to hypothyroid subjects.

As shown in Table 2, Tri-iodothyronine ($p < 0.000$), thyroxine ($p < 0.000$), thyroid stimulating hormone ($p < 0.000$) were significantly different between the groups. Further, tri-iodothyronine, thyroxine levels were significantly low ($p < 0.05$) in hypothyroid group, high ($p < 0.05$) in hyperthyroid subjects when compared to controls. Between group analysis showed that tri-iodothyronine ($p < 0.05$), thyroxine ($p < 0.05$) were significantly high in hyperthyroid subjects when compared to hypothyroid subjects. Thyroid stimulating hormone was significantly high in hypothyroid group ($p < 0.05$) when compared to hyperthyroid subjects.

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Between group and within group differences of NT pro BNP and soluble ST2 were depicted in Table 3. Significant difference was seen in NT pro BNP ($p < 0.000$) and ST2 ($p < 0.001$) between controls, hypothyroid subjects and hyperthyroid subjects. Further within group observations showed significantly higher NT pro BNP ($p < 0.05$) and low ST2 ($p < 0.05$) in hyperthyroid subjects when compared to hypothyroid subjects.

A showed in Table 4, the higher thyroid stimulating hormone levels were positively correlated with, NT pro BNP ($r = 0.537$; $p < 0.000$) and ST2 ($r = 0.42$; $p < 0.000$).

Table 1: Baseline characteristics of controls, hypothyroid and hyperthyroid subjects.

Sl.No	Parameter	Control group(n= 45)	Hypothyroid (n= 45)	Hyperthyroid (n= 45)	P value (ANOVA)
1	Age(yrs)	22.00 ± 3.32	20.69 ± 2.36	20.35 ± 2.27	0.100
2	Height (cm)	165.08 ± 5.27	163.87 ± 6.86	164.88 ± 4.92	0.566
3	Weight(kg)	60.60 ± 6.38	65.58 ± 10.03*	59.34 ± 5.08$^{\#}$	0.000
4	BMI (Kg/m^2)	22.25 ± 2.32	24.38 ± 3.12*	22.81 ± 2.64$^{\#}$	0.000
5	WHR	0.83 ± 0.05	0.88 ± 0.06*	0.81 ± 0.06$^{\#}$	0.000
6	HR (bpm)	82.40 ± 2.78	74.55 ± 3.26*	87.14 ± 6.00$^{@\#}$	0.000
7	SBP (mmHg)	114.00 ± 4.98	120.80 ± 5.91*	122.67 ± 3.70$^{@\#}$	0.000
8	DBP (mmHg)	75.42 ± 2.28	81.60 ± 6.38*	84.40 ± 3.80$^{@\#}$	0.000

Data expressed as Mean ± SD. BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, PP: Pulse Pressure, RPP: Rate Pressure Product, HR: Heart Rate.
*Controls Vs. Hypothyroid subjects; $p < 0.05$.
@ Controls Vs. Hyperthyroids; $p< 0.05$.
# Hypothyroids Vs. Hyperthyroids; $p< 0.05$.

Table 2: Thyroid function tests of controls, hypothyroid and hyperthyroid subjects.

Sl.no	Parameter	Control group(n= 45)	Hypothyroid (n= 45)	Hyperthyroid (n= 45)	P value (ANOVA)
1	fT3 (pmol/L)	5.17 ± 0.82	2.40 ± 0.59*	11.13 ± 2.25$^{@\#}$	0.000
2	fT4 (pmol/L)	12.29 ± 2.28	2.24 ± 1.45*	28.31 ± 3.90$^{@\#}$	0.000
3	TSH (uU/L)	2.27 ± 0.67	10.51 ± 2.79*	0.18 ± 0.09$^{@\#}$	0.000

fT3: Tri-iodothyronine, fT4: Thyroxine, TSH: Thyroid releasing hormone.

Data expressed as Mean ± SD.
*Controls Vs. Hypothyroid subjects; $p < 0.05$.
@ Controls Vs. Hyperthyroids; $p< 0.05$.
# Hypothyroids Vs. Hyperthyroids; $p< 0.05$.

Table 3: N terminal pro BNP and ST2 values of controls, hypothyroid and hyperthyroid subjects.

Sl.no	Parameter	Control group(n= 45)	Hypothyroid (n= 45)	Hyperthyroid (n= 45)	P value (ANOVA)
1	NT pro BNP (pg/ml)	108.50 ± 8.63	234.99 ± 32.24*	293.42 ± 39.24$^{@\#}$	0.000
2	ST 2 (ng/ml)	12.74 ± 1.97	21.98 ± 3.10*	18.24 ± 4.75$^{@\#}$	0.000

Data expressed as Mean ± SD.
*Controls Vs. Hypothyroids ; $p < 0.05$.
@ Controls Vs. Hyperthyroids; $p< 0.05$.
# Hypothyroids Vs. Hyperthyroids; $p< 0.05$.

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Table 4. Association of TSH with NT pro BNP, ST2 in hypothyroid subjects

Sl.No	Parameter	TSH	
		Hypothyroid group	
		r value	**p value**
1	NT pro BNP	0.537	0.000
2	ST2	0.442	0.000

Discussion: This study was carried out to evaluate the Serum Soluble ST2 Receptor and B type natriuretic peptides in thyroid disorders, and to explore the relationship of thyroid stimulating hormone with Serum Soluble ST2 Receptor, B type natriuretic peptides in newly diagnosed hypo and hyper thyroid individuals.

Our study is unique that, as far as we are aware this is the first time that the role of ST2 was exposed in newly diagnosed hypo and hyperthyroid individuals.

In our study as showed in table 1, there was no significant difference in age and height between the groups. But, Weight, Body mass index, heart rate, systolic blood pressure, diastolic blood pressure were significantly different between the groups.

The most remarkable observation to emerge from our study was a significant difference in NT pro BNP and ST2 between controls, hypothyroid subjects and hyperthyroid subjects. Further within group observations showed higher NT pro BNP and low ST2 in hyperthyroid subjects when compared to hypothyroid subjects.

BNP is a prognostically robust tool for risk stratification across the spectrum of acute coronary syndromes and it can reliably predict the presence or absence of left ventricular dysfunction on echocardiogram (8).

A change in BNP levels may be associated with other conditions. Pulmonary disease resulting in right ventricular dysfunction leads to increased BNP values (9).

Although the exact mechanisms of BNP release are still unclear, its release seems to be stimulated by increased LV wall stress and volume expansion (10).

The actual function of BNP is thought to be cardioprotective through increasing natriuresis and diuresis, vasodilatation and direct inhibition of the sympathetic nervous system and the renin--angiotensin system (11).

Changes to these parameters have also been found in patients with thyroid dysfunction. Triiodothyronine decreases systemic vascular resistance by dilating the resistance arterioles of the peripheral circulation (12).

As a result of the decrease in systemic vascular resistance, the ejective arterial filling volume falls, causing an increase in renin release and activation of the angiotensin--aldosterone axis (13). This, in turn, stimulates renal sodium reabsorption, leading to an increase in plasma volume. Thyroid hormone also stimulates erythropoietin secretion. The combined action of these two is an increase in blood volume and preload, which further increases cardiac output (14).

Schultz et al. have shown alterations of NT-proBNP levels across a range of thyroid dysfunctions. Our study assessed whether the previously observed alterations in NT-proBNP levels with thyroid dysfunction are consistent and tries to interpret the results in the light of more recently published data on biological variation of this analyte (15).

ST-2 is a member of the Toll-like/IL-1-receptor superfamily (16). Soluble ST-2 has been extensively studied as a prognostic tool among patients with both acute and chronic heart failure (17). Increased concentrations of soluble ST-2 in patients with acute destabilized heart failure at their initial presentation indicate increased risk of future mortality (18).

Conclusion: This increased N T Pro BNP levels in both newly diagnosed hypo and hyperthyroidism indicates that there will be a left ventricular dysfunction or they may be at risk of development of acute coronary syndromes, and the ST2 is an indicator of indicator of increased risk of future cardiovascular mortality.

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