Study of copeptin and brain natriuretic peptide in patients with thyroid dysfunction: relation to cardiovascular performance

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Received 13 August 2015
Accepted 08 September 2015

Egyptian Journal of Obesity, Diabetes and Endocrinology
2015, 1:65–71

Background
Thyroid disorders are the second most common endocrine disorders after type 2 diabetes mellitus. Copeptin, the C-terminal part of pre-pro arginine vasopressin, and brain natriuretic peptide (BNP) are new markers of cardiac and endothelial diseases. The relationship between thyroid status and copeptin has not been studied yet. Serum BNP levels are also affected by thyroid function status; however, its value in the presence of thyroid dysfunction has been recently questioned.

Aim of the work
The aim of this work was to assess the alteration of serum copeptin and BNP in patients with thyroid dysfunction and the relationship between this alteration and cardiovascular performance in patients with thyroid dysfunction.

Materials and methods
This study included 60 patients who were divided into two groups: group 1 included 30 patients with hyperthyroidism and group 2 included 30 patients with primary hypothyroidism. A total of 20 healthy euthyroid individuals served as the control group (group 3). All patients and controls were subjected to estimation of serum and urine osmolarity and electrolyte study and evaluation of T3, T4, thyroid-stimulating hormone, serum copeptin, and serum BNP using enzyme-linked immunosorbent assay. Echocardiographic study was conducted to assess left ventricle (LV) systolic and diastolic functions. In addition, endothelial function was assessed by measuring flow-mediated dilatation of the brachial artery.

Results
In patients with hyperthyroidism, serum copeptin was significantly lower than that in controls (mean = 2.24 ± 1.68 vs. 3.34 ± 2.93 pmol/l, $P = 0.03$). However, it was significantly higher in hypothyroid patients in comparison with controls (mean = 18.78 ± 11.29 vs. 3.34 ± 2.93 pmol/l, $P = 0.0001$). Serum BNP in the hypothyroid group was significantly higher than that in the control group (mean = 15.02 ± 6.9 vs. 3.60 ± 1.38 ng/l, $P = 0.028$). E'/A' was significantly lower in hypothyroid patients in comparison with the control group (mean = 1.15 ± 0.72 vs. 1.48 ± 0.48, $P = 0.03$), and more than half of the patients (53%) had E'/A' less than 1, suggesting the presence of diastolic dysfunction in hypothyroid patients. There was a significant negative correlation between ejection fraction ($P = 0.002$), fractional shortening ($P = 0.01$), and copeptin in the hypothyroid group. There was a significant positive correlation between copeptin and flow-mediated dilatation ($P = 0.01$) in the hyperthyroid group.

Conclusion
Serum copeptin and BNP were significantly increased in hypothyroid patients, whereas serum copeptin was significantly decreased in hyperthyroid patients. In hyperthyroid patients, LV systolic function was increased. More than half of the hypothyroid patients with high serum copeptin levels had impaired LV filling.

Keywords:
arginine vasopressin, atrial natriuretic peptide, brain natriuretic peptide, complete blood picture, diabetes mellitus, early diastolic velocity, ejection fraction, enzyme-linked immunosorbent assay, late diastolic velocity

Egyptian Journal of Obesity, Diabetes and Endocrinology 1:65–71

2356-8062

Introduction

Copeptin, a novel biomarker that has entered the clinical era, was found to be a stable and sensitive surrogate marker for arginine vasopressin (AVP) [1]. It is the C-terminal part of pre-pro AVP [2]. AVP is unstable in nature and rapidly cleared from plasma.

Copeptin is secreted in equimolar quantities as vasopressin and has the advantage of high stability in blood samples, hence used as a surrogate marker for vasopressin [3]. Brain natriuretic peptide (BNP) is a cardiac hormone released from the myocardium in response to increased ventricular wall tension due to sodium and water retention, volume expansion, and elevated end diastolic volume [4]. Thyroid disorders are the second most common endocrine disorders after type 2 diabetes mellitus [5]. Clinical presentation is often vague and nonspecific with multiple complications affecting various body systems, the diagnosis of which is often dependent on laboratory investigations [6]. The relationship between circulating level of copeptin and thyroid status has not been studied yet. However, available studies concern the relationship between AVP and thyroid function. Both hyperthyroidism and hypothyroidism are associated with marked effects on the cardiovascular system, including changes in cardiac output, blood pressure, and systemic vascular resistance. Besides, impaired thyroid function is accompanied by changes in plasma vasopressin levels [7]. Moreover, copeptin has been correlated with endothelial function in humans [8]. Serum BNP levels are affected by thyroid function status [9]. It has been found that thyroid hormones directly increase the myocardial gene expression of natriuretic peptides, as well as directly modulate atrial natriuretic peptide and BNP synthesis, as suggested by an increased cellular mRNA content; consequently, natriuretic peptide levels change in different thyroid function states [10]. BNP has a direct relaxant effect on vascular smooth muscle cells, regulates the intravascular volume, influences electrolyte and fluid balance, and mediates direct effects on endothelial permeability in the vasculature [11].

Materials and methods

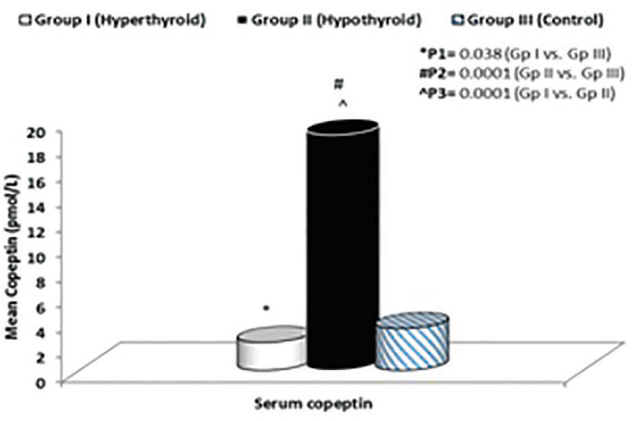
This study was carried out on 60 patients who attended the endocrine outpatient clinic of the Main Alexandria University Hospital. They were divided into two groups: group 1 included 30 patients with hyperthyroidism and group 2 included 30 patients with primary hypothyroidism. Group 3 included 20 healthy euthyroid individuals (the control group). Exclusion criteria were as follows: drug-induced thyroid dysfunction, diabetes mellitus, unstable angina, acute heart failure, acute myocardial infarction, renal failure, liver failure, pulmonary embolism, and pregnancy. All patients and controls were subjected to history taking and clinical examination, including cardiac examination, peripheral pulse, and blood pressure. Laboratory investigations included routine investigations (complete blood picture, liver function tests, and renal function tests) and specific investigations [serum total T3, T4, and thyroid-stimulating hormone (TSH), serum copeptin, and serum BNP using enzyme-linked immunosorbent assay]. Echocardiography was carried out using HD11XE echo machine (Philips, USA): (a) transthoracic M-mode echocardiography for the assessment of left ventricle (LV) function by measuring ejection fraction (EF) and fractional shortening (FS), and assessment of LV filling using transmitral pulsed Doppler flow to detect E and A. (b) Mitral annular pulsed tissue Doppler imaging for assessment of S, E', and A'. Flow-mediated dilatation (FMD) of the brachial artery was carried out using B-mode ultrasound to assess the endothelial function: a sphygmomanometric (blood pressure) cuff was placed above the antecubital fossa and baseline rest ultrasonographic image of the brachial artery diameter was acquired. Thereafter, arterial occlusion was created by means of cuff inflation to 50 mmHg suprasystolic pressure to occlude arterial inflow for 5 min. Another image was obtained at 60 s after cuff release:

$$\text{Flow mediated dilatation (\%)} = \frac{\text{Brachial artery diameter after cuff release} - \text{baseline brachial artery diameter}}{\text{Baseline brachial artery diameter}} \times 100.$$

Results

There was a significant decrease in serum copeptin in the hyperthyroid group in comparison with the control group (mean = 2.24 ± 1.68 vs. 3.34 ± 2.93 pmol/l, $P = 0.03$), whereas there was a significant increase in serum copeptin in the hypothyroid group in comparison with the control group (mean = 18.78 ± 11.29 vs. 3.34 ± 2.93 pmol/l, $P = 0.0001$) (Table 1 and Figs. 1 and 2). Serum BNP in the hyperthyroid group was within the reference range in all patients (mean = 3.35 ± 0.7 ng/l) and there was no significant difference between serum BNP levels in the hyperthyroid and control groups,

Figure 1



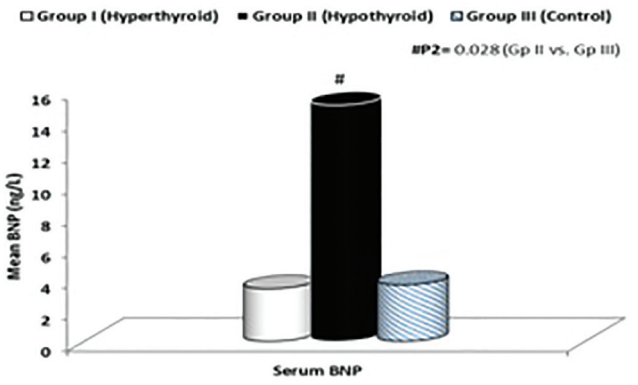
Comparison between the three studied groups as regards copeptin.

whereas there was a significant increase in serum BNP in the hypothyroid group in comparison with the control group (mean = 15.02 ± 6.9 vs. 3.60 ± 1.38, $P = 0.028$). There was a significant negative correlation between serum copeptin and T4 in the hypothyroid group ($P = 0.007$, Fig. 3).

Echocardiographic results

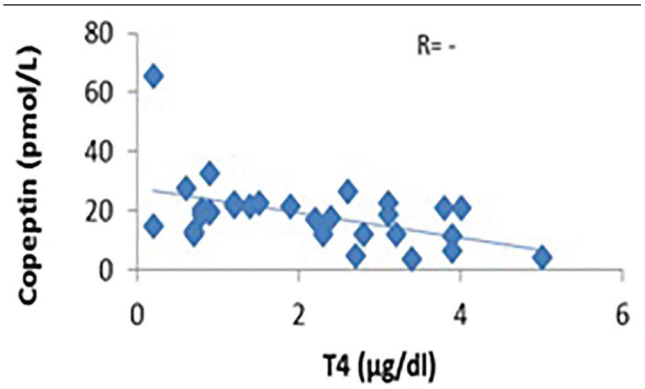
In the hyperthyroid group (Table 2 and Fig. 4) EF was higher than that in the control group, yet this did not reach statistical significance, whereas FS was significantly higher than that in the control group (mean = 38.19 ± 5.14 vs. 33.18 ± 5.50%, $P = 0.003$). LV diastolic filling as assessed with transmitral pulsed Doppler flow (Table 3) revealed that there was no significant difference in E/A ratio between the hyperthyroid group and the control group. Tissue Doppler results (Table 4) revealed that there was no significant difference in E'/A' and S-wave between the hyperthyroid group and the control group. In the hypothyroid group (Table 2 and Fig. 3), there was no significant difference in EF compared with the control group, whereas FS despite being within normal range was significantly higher than that in the control group (mean = 38.25 ± 6.76 vs. 33.18 ± 5.50%, $P = 0.001$). There was a significant negative correlation between copeptin and EF ($P = 0.002$, Fig. 5), as well as copeptin and FS ($P = 0.01$, Fig. 6). E'/A' was significantly lower in hypothyroid patients in comparison with the control group (mean = 1.15 ± 0.72 vs. 1.48 ± 0.48, $P = 0.03$), and more than half of the patients (53%) had E'/A' less than 1, suggesting the presence of diastolic dysfunction in hypothyroid patients (Table 4 and Fig. 7). The velocity of S-wave was lower in the hypothyroid group than in the control group; however, there was no statistical significance (Table 4).

Figure 2



Comparison between the three studied groups as regards brain natriuretic peptide (BNP).

Figure 3



Correlation between serum copeptin and serum T4 in the hypothyroid group.

Table 1 Comparison between the three studied groups as regards copeptin and brain natriuretic peptide

Serum copeptin and BNP	Group 1 (hyperthyroid)	Group 2 (hypothyroid)	Group 3 (control)	
Serum copeptin (pmol/l)				
Range	0.0–6.0	3.8–65.7	0.0–11.8	$P_1 = 0.038 P_2 = 0.0001 P_3 = 0.0001$
Mean ± SD	2.24 ± 1.68	18.78 ± 11.29	3.34 ± 2.93	
Serum BNP (ng/l)				
Range	0.0–16.1	0.1–181.3	0.1–25.1	$P_1 = 0.120 P_2 = 0.028 P_3 = 0.068$
Mean ± SD	3.35 ± 0.7	15.02 ± 6.9	3.60 ± 1.38	

BNP, brain natriuretic peptide; P_1: comparison between group 1 and 3; P_2: comparison between group 2 and 3; P_3: comparison between group 1 and 2; P value is significant if less than 0.05.

Table 2 Comparison between the three studied groups as regards echocardiographic findings

Echocardiography	Group 1 (hyperthyroid)	Group 2 (hypothyroid)	Group 3 (control)	
EF (%)				
Range	53.0–84.0	42.0–81.0	60.0–78.0	$P_1 = 0.207 P_2 = 0.463 P_3 = 0.206$
Mean ± SD	69.47 ± 6.68	67.93 ± 7.66	68.10 ± 5.01	
FS (%)				
Range	26.4–46.9	20.7–50.0	22.0–46.3	$P_1 = 0.003 P_2 = 0.001 P_3 = 0.485$
Mean ± SD	38.19 ± 5.14	38.25 ± 6.76	33.18 ± 5.50	

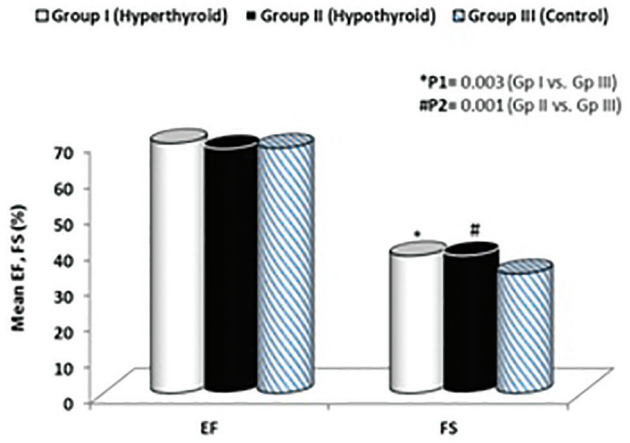
EF, ejection fraction; FS, fractional shortening; P_1: comparison between group 1 and 3; P_2: comparison between group 2 and 3; P_3: comparison between group 1 and 2; P value is significant if less than 0.05.

Table 3 Comparison between the three studied groups as regards transmitral pulsed Doppler flow

Transmitral pulsed Doppler flow	Group 1 (hyperthyroid)	Group 2 (hypothyroid)	Group 3 (control)	
E (m/s)				
Range	0.0–1.4	0.3–1.0	0.6–1.3	$P_1 = 0.428 P_2 = 0.018 P_3 = 0.005$
Mean ± SD	0.88 ± 0.29	0.74 ± 0.21	0.89 ± 0.19	
A (m/s)				
Range	0.0–1.1	0.2–1.0	0.4–9.8	$P_1 = 0.143 P_2 = 0.157 P_3 = 0.130$
Mean ± SD	0.67 ± 0.19	0.61 ± 0.22	1.14 ± 2.04	
E/A				
Range	0.6–3.4	0.1–3.9	0.9–2.0	$P_1 = 0.232 P_2 = 0.382 P_3 = 0.391$
Mean ± SD	1.42 ± 0.64	1.37 ± 0.78	1.32 ± 0.28	

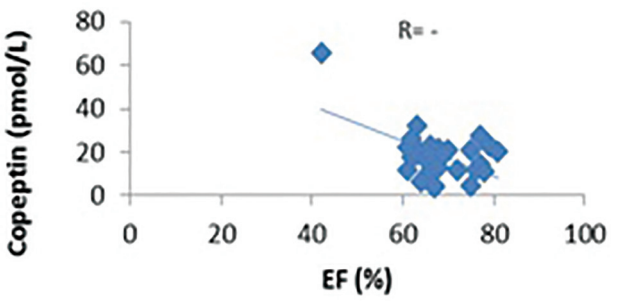
P_1: comparison between group 1 and 3; P_2: comparison between group 2 and 3; P_3: comparison between group 1 and 2; P value is significant if less than 0.05.

Figure 4



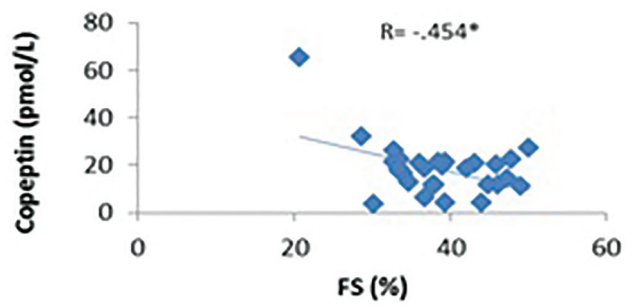
Comparison between the three studied groups as regards echocardiographic findings.

Figure 5



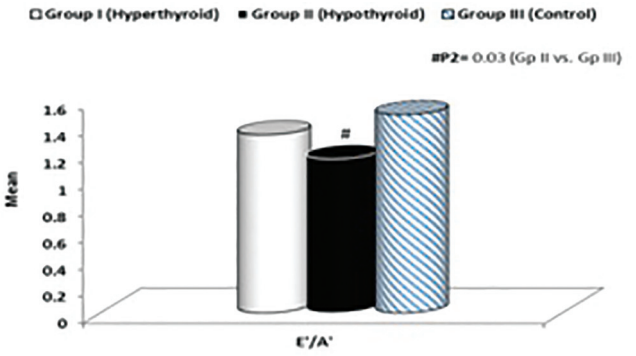
Correlation between serum copeptin and serum ejection fraction (EF) in the hypothyroid group.

Figure 6



Correlation between serum copeptin and serum fractional shortening (FS) in the hypothyroid group.

Figure 7



Comparison between the three studied groups as regards mitral annular pulsed tissue Doppler diastolic function.

Endothelial function results

The results of the study of FMD of the brachial artery (Table 5 and Fig. 8) revealed that there was a significant decrease in FMD in the hyperthyroid and hypothyroid groups in comparison with the control group, suggesting the presence of endothelial dysfunction in patients with thyroid disorders. In the hyperthyroid group, there was a significant positive correlation between copeptin and FMD (Fig. 9).

Discussion

Copeptin, the C-terminal portion of pre-pro AVP, is a polypeptide comprising 39 amino acids. It is a neurohormone of the AVP system that is cosecreted with AVP from the hypothalamus. Copeptin has recently come into clinical practice and has been regarded as a novel neurohormone [12]. BNP, a 32 amino acid peptide produced in ventricular cardiomyocytes, is secreted in response to volume expansion or pressure overload. It induces natriuresis and vasodilatation along with an inhibitory effect on the renin–angiotensin–aldosterone

Table 4 Comparison between the three studied groups as regards mitral annular pulsed tissue Doppler systolic and diastolic functions

Pulsed tissue Doppler	Group 1 (hyperthyroid)	Group 2 (hypothyroid)	Group 3 (control)	
E' (m/s)				
Range	0.1–0.3	0.0–0.7	0.1–0.9	$P_1 = 0.054 P_2 = 0.144 P_3 = 0.239$
Mean ± SD	0.14 ± 0.05	0.16 ± 0.17	0.23 ± 0.23	
A' (m/s)				
Range	0.1–0.3	0.0–0.8	0.0–0.8	$P_1 = 0.116 P_2 = 0.450 P_3 = 0.045$
Mean ± SD	0.11 ± 0.04	0.16 ± 0.15	0.17 ± 0.20	
E'/A'				
Range	0.6–2.0	0.2–4.0	1.1–3.2	$P_1 = 0.122 P_2 = 0.03 P_3 = 0.116$
Mean ± SD	1.33 ± 0.38	1.15 ± 0.72	1.48 ± 0.48	
S (m/s)				
Range	0.1–0.4	0.0–0.2	0.1–0.2	$P_1 = 0.185 P_2 = 0.060 P_3 = 0.042$
Mean ± SD	0.11 ± 0.06	0.09 ± 0.02	0.10 ± 0.02	

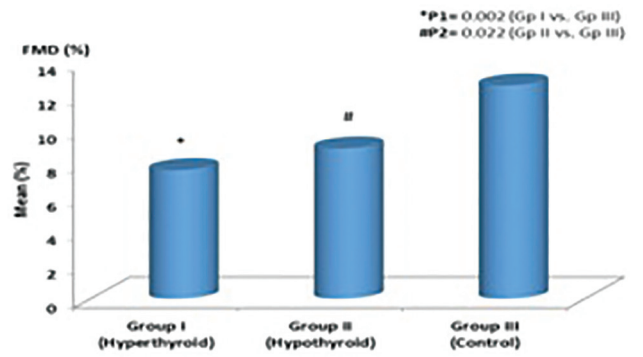
P_1: comparison between group 1 and 3; P_2: comparison between group 2 and 3; P_3: comparison between group 1 and 2; *P* value is significant if less than 0.05.

Table 5 Comparison between the three studied groups as regards flow-mediated dilatation of the brachial artery

Flow-mediated dilatation of the brachial artery	Group 1 (hyperthyroid)	Group 2 (hypothyroid)	Group 3 (control)	
FMD (%)				
Range	0.0–25.0	1.96–36.0	2.2–21.6	$P_1 = 0.002 P_2 = 0.022 P_3 = 0.223$
Mean ± SD	7.60 ± 5.5	8.88 ± 7.21	12.61 ± 5.49	

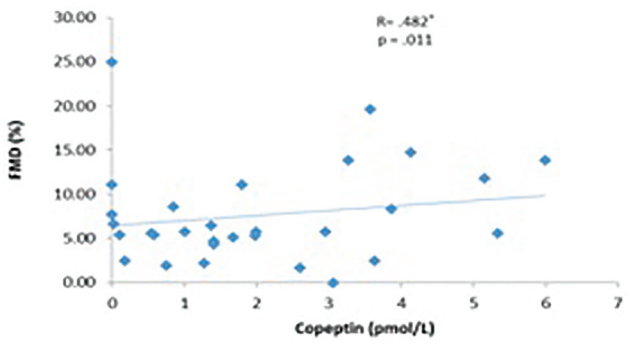
FMD, flow-mediated dilatation; P_1: comparison between group 1 and 3; P_2: comparison between group 2 and 3; P_3: comparison between group 1 and 2; *P* value is significant if less than 0.05.

Figure 8



Comparison between the three studied groups as regards flow-mediated dilatation (FMD).

Figure 9



Correlation between serum copeptin and flow-mediated dilatation (FMD) in the hyperthyroid group.

and adrenergic systems [13]. Thyroid hormones serve as master regulators for diverse remodeling processes of the cardiovascular system. Optimal levels of thyroid hormones both in the circulation and in cardiac tissues are critical for normal homeostasis [14]. The endothelial system acts as a large endocrine organ in the human body; however, little is still known about the regulative role of thyroid hormones on endothelial cells [15].

Serum copeptin and thyroid dysfunction

In the current study, serum copeptin in patients with hyperthyroidism was significantly lower than that in controls (mean = 2.24 ± 1.68 vs. 3.34 ± 2.93 pmol/l, *P* = 0.03) and in hypothyroid patients (mean = 2.24 ± 1.68 vs. 18.78 ± 11.29 pmol/l, *P* = 0.0001). Moreover, Harvey *et al.* [16] found that the osmolar thresholds for the onset of thirst sensation and AVP release were reduced in the thyrotoxic state. Further, Marcisz *et al.* [17] demonstrated increased plasma AVP level in patients with hyperthyroidism. The decrease in serum copeptin in hyperthyroid patients, observed in the present study, might explain the polyuria described in hyperthyroid states. Serum osmolarity is normal in these patients indicating that the decrease in vasopressin release is not due to osmolar stimuli but mostly due to the direct effect of the increased thyroid hormone level. On the basis of the present study, serum copeptin level was significantly

higher in hypothyroid patients in comparison with controls (mean = 18.78 ± 11.29 vs. 3.34 ± 2.93 pmol/l, $P = 0.0001$) and hyperthyroid patients (mean = 18.78 ± 11.29 vs. 2.24 ± 1.68 pmol/l, $P = 0.0001$). About 70% of hypothyroid patients had elevated copeptin level above the upper limit of normal. There was a significant negative correlation between copeptin and T4 ($P = 0.007$) and a positive correlation between copeptin and TSH; however, this did not reach statistical significance. In accordance with the current results, Skowsky and Kikuchi [18] showed that plasma AVP was elevated in patients with hypothyroidism. Similarly, Nakano *et al.* [19] have noted the augmentation of antidiuretic hormone level in the state of hypothyroidism and reported that patients with hypothyroidism showed hyponatremia and elevated plasma vasopressin without hypovolemia, and laboratory findings and the clinical signs were similar to syndrome of inappropriate antidiuretic hormone secretion. In the present study, the significant inverse relationship between serum T3 and T4 and serum copeptin in the three groups, as well as the significant direct relation of TSH and copeptin confirm the inhibitory effect of thyroid hormones on neurohypophysial release of vasopressin. The suggested effect of cardiac output on vasopressin release in patients with thyroid dysfunction is almost excluded in our study, considering the normal EF in the three groups.

Serum brain natriuretic peptide and thyroid dysfunction

In the present study, serum BNP in the hyperthyroid group was within the reference range in all patients and was lower than that in the control group (mean = 3.35 ± 0.7 vs. 3.60 ± 1.38 ng/l, $P = 0.120$), yet this did not reach statistical significance. Similarly, Wei *et al.* [20] found that BNP level remained unchanged in patients with hyperthyroidism with normal LV function and that increased BNP level was found only in patients with clinical and echocardiographic evidence of LV dysfunction. The normal level of serum BNP in our patients with hyperthyroidism can be attributed to the absence of ventricular dilatation and decrease in EF or FS in them. The lack of correlation between BNP and thyroid function tends to explain the indirect effect of thyroid hormones on BNP. In the present study, serum BNP in the hypothyroid group was significantly higher than that in the control group (mean = 15.02 ± 6.9 vs. 3.60 ± 1.38 ng/l, $P = 0.028$). In accordance with the current results, Perez *et al.* [21] found that hypothyroid patients were more likely to have higher NT-proBNP levels. In contrast, Schultz *et al.* [22] showed that NT-proBNP is decreased in hypothyroid patients and is elevated with treatment. In the present study, in line with the results of Huang *et al.* [23], the rise in BNP was mostly due to the increase in TSH acting directly on cardiac myocytes. However, elevation of BNP in patients with hypothyroidism may represent a warning signal for future cardiovascular disease and may be an early marker of diastolic dysfunction, although this is not supported by the lack of correlation between BNP and E/A and E'/A'.

Serum copeptin and brain natriuretic peptide: relationship with echocardiographic findings

In the present study, in hyperthyroid patients, LV systolic function was increased, whereas diastolic function was not changed; these changes showed correlation neither with serum copeptin nor with serum BNP. However, more than half of the hypothyroid patients with elevated serum copeptin levels had impaired LV filling as shown by E'/A' less than 1. Morgenthaler [24] found that LV EF was decreased in patients with high AVP levels after myocardial infarction. Kelly *et al.* [25] documented that copeptin concentrations were significantly related to the degree of LV dysfunction after myocardial infarction and showed that copeptin correlated inversely with LVEF at discharge ($P<0.001$) and follow-up ($P<0.001$). In the present study, hypothyroid patients with diastolic dysfunction, as evidenced by E'/A' less than 1, had increased serum copeptin level, a fact that may suggest the relationship between copeptin and diastolic dysfunction in hypothyroid patients. In accordance with the present study, Erkan *et al.* [26] revealed significantly decreased E'/A' ratio in patients with subclinical hypothyroidism compared with euthyroid controls. Franzoni *et al.* [27] also found lower E'/A' ratio in patients with subclinical hypothyroidism.

Serum copeptin and brain natriuretic peptide: relationship with endothelial function

The present study revealed that FMD in patients with hyperthyroidism was significantly lower than that in controls (mean = 7.60 ± 5.54 vs. 12.61 ± 5.49%, $P = 0.002$), suggesting the presence of arterial stiffness and endothelial dysfunction in hyperthyroid patients. There was a significant positive correlation between copeptin and FMD ($P = 0.01$), which suggests that the decrease in copeptin level and endothelial dysfunction observed in hyperthyroidism may be due to the direct effect of increased thyroid hormones. In agreement with the results of the current study, Palmieri *et al.* [28] found that total arterial stiffness is increased in overt hyperthyroid patients. Verma *et al.* [29] found that nitric oxide levels were significantly lower in hyperthyroidism than in controls, which is an important mechanism for endothelial dysfunction in patients with hyperthyroidism. In the current study, FMD in patients with hypothyroidism was significantly lower than that in controls (mean = 8.88 ± 7.21 vs. 12.61 ± 5.49%, $P =$

0.022), denoting the presence of endothelial dysfunction in hypothyroid patients. In accordance with the present result, Tudoran and Tudoran [30] assessed the endothelial function in patients with hypothyroidism using FMD, which revealed that FMD was significantly decreased in all hypothyroid patients compared with controls. Masaki *et al.* [31] found that high NT-proBNP was associated with raised arterial stiffness in subclinical hypothyroidism and that subclinical hypothyroidism may be a risk factor for cardiovascular events related to arterial stiffening and LV diastolic dysfunction.

Conclusion

Serum copeptin varies with different thyroid function states. It was significantly decreased in hyperthyroid patients and significantly increased in hypothyroid patients. Serum BNP was significantly increased in hypothyroid patients. Study of LV functions in hyperthyroid patients showed increased systolic function as evidenced by high EF and FS (assessed with M-mode echocardiography) and high S-wave velocity (assessed with pulsed tissue Doppler). In hyperthyroid patients, LV functions showed a significant correlation neither with serum copeptin nor with serum BNP. Hypothyroid patients, especially those with high serum copeptin level, had impaired LV filling on tissue Doppler echocardiographic study, suggesting a relation between serum copeptin and diastolic dysfunction. Patients with thyroid disorders showed endothelial dysfunction, suggesting a relationship between serum copeptin and endothelial dysfunction.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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