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ORIGINAL ARTICLE

Relationships between serum levels of thyroid hormones and serum concentrations of asymmetric dimethylarginine (ADMA) and *N*-terminal-pro-B-type natriuretic peptide (NT-proBNP) in patients with Graves' disease

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Abstract Endothelial dysfunction as well as abnormal thyroid hormone levels may be responsible for increased cardiovascular risk in Graves' disease (GD). Asymmetric dimethylarginine (ADMA) and *N*-terminal-pro-B-type natriuretic peptide (NT-proBNP) are new markers of endothelial and myocardial dysfunction, respectively. The purpose of this study was to investigate the relationship among the serum levels of ADMA, NT-proBNP, and thyroid hormones in GD patients. This was a cross-sectional investigation conducted in a university teaching hospital. Two hundred and thirty-nine GD (Female: 182, Male: 57) patients and 81 normal controls were enrolled in this study. Serum levels of ADMA were positively related with FT3 ($r = 0.584$, $P < 0.001$), FT4 ($r = 0.551$, $P < 0.001$), and TRAb levels ($r = 0.502$, $P < 0.001$). Serum NT-proBNP levels were positively associated with FT3 ($r = 0.243$, $P < 0.001$) and FT4 levels ($r = 0.274$, $P < 0.001$), as well as heart rate ($r = 0.271$, $P < 0.03$). The elevation of serum ADMA and NT-proBNP levels were also observed in patients with controlled hyperthyroidism. It is thus concluded that serum ADMA and NT-proBNP levels were increased in GD patients. Future studies may determine the usefulness of these two biomarkers to detect early signs of endothelial dysfunction, vascular stiffness, and fluid volume in GD patients.

Keywords ADMA · NT-proBNP · Hyperthyroidism · Graves' disease

Introduction

Thyroid hormones play an important role in modulating cardiac function and cardiovascular hemodynamics. Graves's disease (GD) is the most common cause of hyperthyroidism, which is associated with many cardiovascular symptoms and signs, such as atrial fibrillation, cardiac arrhythmias, and heart failure [1].

Vascular endothelial dysfunction and vascular stiffness, as well as other factors are thought to contribute to the pathogenesis of cardiovascular diseases [2]. Nitric oxide (NO) is a potent vasodilator and a principal mediator regulating vascular homeostasis [3]. Asymmetric dimethylarginine (ADMA), derived from the catabolism of proteins containing methylated arginine residues, can inhibit NO synthesis [4]. Elevated circulating ADMA levels have been shown to be related with increasing age, diabetes, gestational diabetes, hypertension, obesity, and many other clinical conditions [4–7]. In addition, changes in ADMA levels are also associated with cerebral and cardiovascular events, as well as all-cause mortality [4, 7, 8]. ADMA is now recognized as a novel risk factor for endothelial dysfunction and cardiovascular diseases [9].

Cardiac natriuretic hormones (CNH) are substances with similar effects as NO. These hormones mainly include the atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), which are secreted in response to mechanical wall stretch or neuro-hormonal stimulation by atrial and ventricular myocytes, respectively [10]. CNH exerts diuretic, natriuretic, vasodilator, and anti-inflammatory effects. Paradoxically, increased circulating CNH levels, especially

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BNP levels, have been seen in patients with chronic heart failure and other noncardiac disorders, such as renal failure [11] and severe sepsis [12], thereby indicating a resistance to the biological action of CNH, and its elevation may alert the clinician that the heart is under a state of stress [10, 13]. *N*-terminal pro-B-type natriuretic peptide (NT-ProBNP) is the inactive cleavage product of BNP, and it can reflect the presence of body volume overload and vascular stiffness [14]. Since it has a longer half-life and greater stability than BNP, NT-proBNP is more suitable for clinical applications. It is now considered to be an index for activation of the neuroendocrine system and myocardial dysfunction [10].

Thyroid hormones have direct effects on cardiac myocytes, endothelial cells, and vascular smooth muscle cells [15, 16], resulting in hypertrophy and stiffness of the vessels [17]. The elevations of circulating ADMA and NT-proBNP were observed not only in hyperthyroid patients but also in healthy subjects with acutely induced hyperthyroidism [18–21]. Although both hyper- and hypothyroidism patients had impaired endothelial function, the increases of ADMA and NT-proBNP were more pronounced in patients with hyperthyroidism [18, 21, 22].

Thus, it is quite useful to take serum levels of ADMA and NT-proBNP as surrogate markers to evaluate cardiovascular risk in patients with hyperthyroidism. The purpose of this study was to elucidate the interrelationships among serum levels of ADMA and NT-proBNP in a cohort of GD patients.

Results

Clinical characteristics of the GD patients

Graves' Disease patients had significant elevated levels of circulating ADMA and NT-proBNP as compared with normal controls. (Table 1) No differences between the male and female patients were found in age, serum concentrations of FT3, FT4, TSH, TRAb, ADMA, and NT-proBNP, as well as heart rate and blood pressure (Data not shown), except for a higher BMI (21.8 ± 0.5 vs. 20.6 ± 0.3 kg/m^2, $P = 0.022$) and more smokers (36.8 vs. 0.6%, $P < 0.001$) being seen in male patients.

Correlations between serum levels of ADMA, NT-proBNP with anthropometric parameters, thyroid hormones, and TRAb concentrations

Spearman association analysis showed that in patients with GD, serum ADMA level was positively associated with FT3 ($r = 0.584$, $P < 0.001$) (Fig. 1a), FT4 ($r = 0.551$, $P < 0.001$) (Fig. 1b) and TRAb ($r = 0.502$, $P < 0.001$) (Fig. 1c), whereas it was negatively associated with BMI ($r = -0.220$, $P < 0.005$) and TSH ($r = -0.552$, $P < 0.001$), and was not related to serum NT-proBNP. Serum ADMA concentration showed a positive relationship with heart rate ($r = 0.222$, $P = 0.061$) and systolic blood pressure($r = 0.275$, $P = 0.053$) with marginal significance.

Similarly, the serum NT-proBNP level was positively related to FT3 ($r = 0.243$, $P < 0.001$), FT4 ($r = 0.274$, $P < 0.001$), and heart rate ($r = 0.271$, $P < 0.03$), but inversely related to TSH ($r = -0.155$, $P < 0.02$).

The positive relationships between FT3 and FT4 with ADMA and NT-proBNP remained significant even after the adjustment of age, gender, smoking, and BMI. In multiple regression analysis with ADMA as the dependent variable, it demonstrated that only FT4 contributed to the regression equation ($R^2 = 0.292$, adjusted $R^2 = 0.276$, $P < 0.001$).

Table 1 Clinical characteristics of GD patients and normal controls

	GD patients	Normal controls
n	239	81
Age (Year)	37.3 ± 0.83	35.3 ± 0.8
Female: male	182: 57 (3.2:1)	63:18 (3.5:1)
BMI (kg/m^2)	20.9 ± 0.2	21.2 ± 0.2
Serum FT3 (pmol/l)	14.73 ± 0.89[a]	4.21 ± 0.05
Serum FT4 (pmol/l)	26.95 ± 1.10[a]	13.64 ± 0.14
Serum TSH (μIU/ml)	0.564 ± 0.155[a]	0.741 ± 0.083
Serum TRAb (u/l)	14.91 ± 0.81[a]	0.56 ± 0.07
Serum ADMA (μmol/l)	0.743 ± 0.026[a]	0.394 ± 0.015
Serum NT-proBNP (fmol/ml)	444.4 ± 17.1[a]	312.7 ± 15.8

[a] As compared with normal controls, $P = 0.000$

Comparison of serum ADMA and NT-proBNP concentrations in GD patients with different levels of serum FT4 and normal controls

GD patients were classified into the following three groups according to their serum FT4 levels: FT4 < 20 pmol/l (normal range); 20 ≤ FT4 < 40 pmol/l and FT4 ≥ 40 pmol/l.

Serum levels of ADMA ($P < 0.001$) and NT-proBNP ($P < 0.003$) were significantly different among the GD patients with different FT4 concentrations. It was noteworthy that even in patients with normal FT4 levels (<20 pmol/l), their serum concentrations of ADMA and NT-proBNP were still significantly higher than normal controls (Fig. 2a, b).

Discussion

This study clearly demonstrated that both serum ADMA and NT-proBNP concentrations were significantly associated with thyroid function in GD patients, not influenced by gender, age, BMI, and smoking.

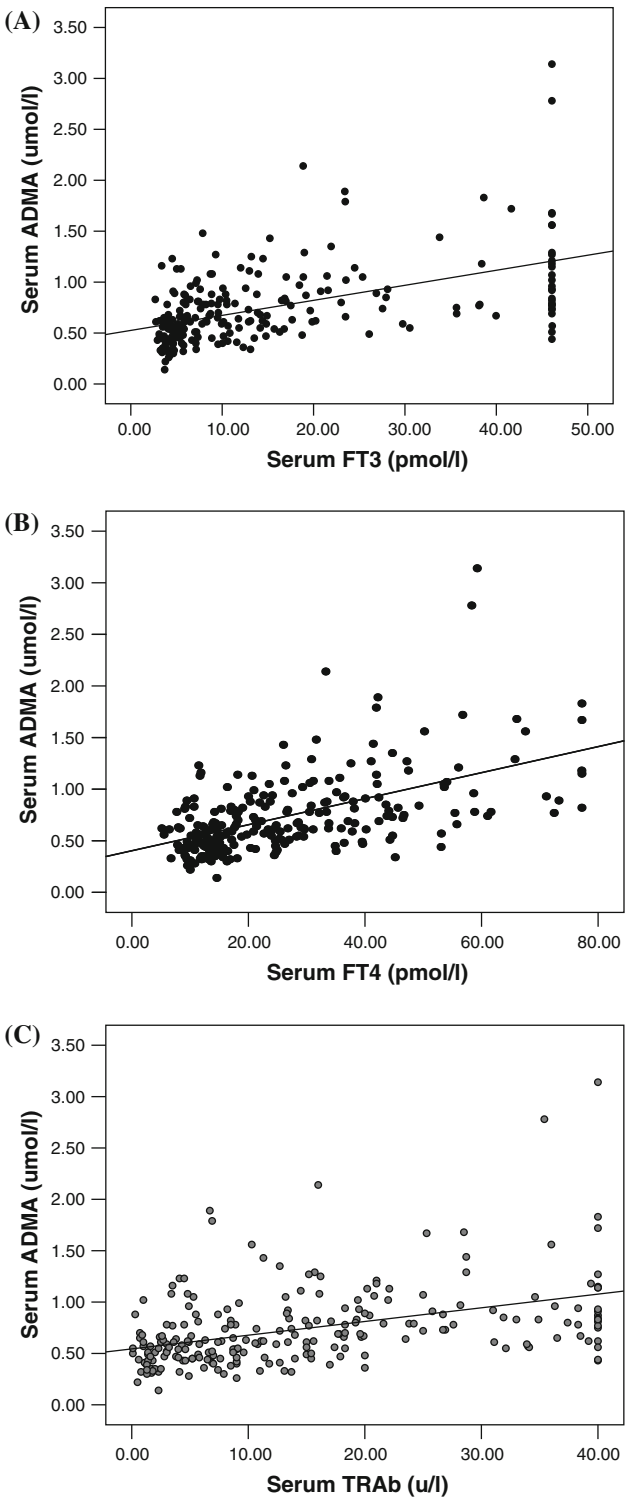

Fig. 1 Relationships between serum FT3 (**a**), FT4 (**b**), TRAb (**c**) and ADMA levels in GD patients

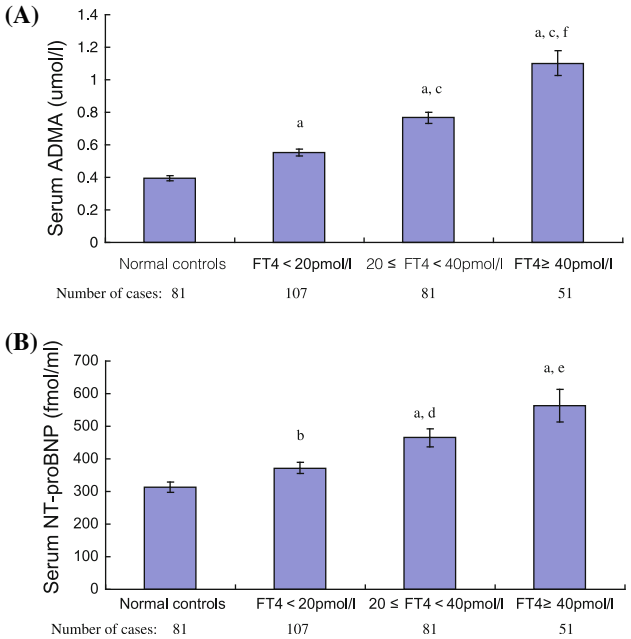

Fig. 2 Serum ADMA (**a**) and NT-proBNP (**b**) levels in GD patients with different serum FT4 levels and normal controls. Compared with normal controls; **a** $P < 0.001$, **b** $P < 0.02$. Compared with GD patients with FT4 < 20 pmol/l, **c** $P < 0.001$, **d** $P < 0.05$, **e** $P < 0.005$. Compared with GD patients with 20 ≤ FT4 < 40 pmol/l, **f** $P < 0.001$

Hyperthyroidism has been shown to be associated with a higher risk of cardiovascular and cerebrovascular mortality [23]. Endothelial dysfunction seems to be one of the pathogenic factors [24], changes in NO, NO synthase (NOS) and ADMA may be responsible in part for this abnormality [18]. It was found that ADMA concentrations were significantly higher in hyperthyroid patients, and serum FT4 levels were positively related with ADMA, but inversely correlated with NO production [18]. Our results also demonstrated a parallel increase in serum ADMA levels along with FT4, FT3, and TRAb values. The possible mechanism for this observation was not investigated in this study. It was demonstrated that endothelial isoform of NO synthase was abundantly expressed in human thyroid gland, especially in thyroid tissues from hyperthyroid patients [25], and human thyrocytes could really release ADMA [26]. Since the thyroid blood flow in hyperthyroid patients is significantly increased, the overproduction of ADMA in hyperthyroidism might also be a compensatory mechanism to reduce NO production and peripheral vasodilatation [18].

ADMA can modulate endothelial cell motility [27], and systemic administration of ADMA could reduce arterial compliance and cerebral blood flow with a concomitant increase of arterial stiffness [28]. Even in young adults aged between 15 and 50 years, ADMA levels were associated increased risk of ischemic stroke [29]. It was thus suggested that ADMA could be better used as a diagnostic marker for vascular risk assessment [30].

The increased serum NT-proBNP levels in GD patients found in this study were in accordance with previous findings [21, 31]. Thyroid hormone can directly stimulate

cardiomyocytes and result in over-production of BNP [20, 22, 32]. The higher heart rate in hyperthyroid patients may shorten the cardiac diastole phase and lead to insufficient subendocardial perfusion. Such an ischemic change has been shown to be accompanied by an elevation of circulating NT-proBNP levels [14]. The positive relationship between serum NT-proBNP levels and heart rate found in our GD patients also supports this postulation.

Clinical evidences have shown that in hyperthyroid patients or in a cohort of old population without prevalent cardiovascular diseases, the arterial stiffness were independently associated with circulating NT-proBNP levels [14, 33]. Although the relationship between serum NT-proBNP and ADMA levels was not observed, the steady increase of both parameters along with the elevation of thyroid hormone levels noted in our study suggested that thyroid hormones may affect the vascular compliance either directly through vascular smooth muscle cells, or indirectly by influencing the release of NO from endothelial cells [23].

Another novel finding derived from our study was that in GD patients with normal FT4 levels, their serum concentrations of ADMA and NT-proBNP were still higher than those of normal controls. We are not clear whether this phenomenon indicated that even the GD patients with controlled hyperthyroidism were still at risk of cardiovascular disease. It has been reported that acute dyspnea patients with persistent elevated NT-proBNP levels after 30 days of discharge may predict 1-year mortality and heart-failure hospitalization [34]. The clinical relevance of the increased serum ADMA and NT-proBNP levels in euthyroid GD patients should be further investigated in prospective and intervention studies.

There are several limitations in this study. It was not a prospective study, and there was no hard end-point of cardiovascular events. Thus, the dynamic changes of serum levels of ADMA and NT-proBNP along with the thyroid hormones were lacking, and the predictive value of serum ADMA and NT-proBNP levels for the development of cardiovascular diseases could not be evaluated. In addition, an echocardiography, carotid artery intima-media thickness (IMT), internal carotid/bulb IMT, or other methods to assess cardiac structure/function and systemic vascular stiffness were not performed.

In conclusion, serum levels of ADMA and NT-proBNP were both increased in hyperthyroid and even euthyroid GD patients. Future studies may determine the usefulness of these two biomarkers to detect early signs of endothelial dysfunction, vascular stiffness, and fluid volume in GD. The direct contribution of increased ADMA and NT-proBNP levels to cardio-vascular end-points in hyperthyroid patients needs to be investigated in prospective studies.

Materials and methods

The GD patients were consecutively recruited from the Department of Endocrine and Metabolic Diseases, Rui-jin Hospital, Shanghai. GD was identified by the presence of clinical symptoms and signs with biochemical confirmation of hyperthyroidism, which was characterized by an elevated serum free thyroxine (FT4) and/or free triiodothyronine (FT3), suppressed thyroid-stimulating hormone (TSH) levels, increased circulating thyroid-stimulating hormone receptor antibody (TRAb) concentrations and/or diffusely elevated thyroidal radioactive Technetium-99 or iodine uptake.

In the screening phase of this study, GD patients with a history of cardiac disease, hypertension, diabetes mellitus or impaired glucose regulation, and renal and hepatic diseases were excluded. Then, the patients were performed an oral glucose tolerance test. In 269 initially screened GD patients, 30 were found to have impaired glucose regulation or diabetes mellitus. These 30 patients were thus excluded from this study. Thus, a total of 239 GD patients (182 female and 57 male) with normal glucose tolerance were enrolled. Among them, 77 were newly onset cases. The remaining patients were on antithyroid drug treatment.

Eighty-one gender-, age- and BMI-matched euthyroid healthy subjects without diabetes, hypertension, renal, hepatic disorders, and with no clinical evidence or a family history of autoimmune diseases were selected as normal controls after a questionnaire survey and reviewing patient history, physical examination, and confirming normal serum concentrations of FT3 (2.63–6.49 pmol/l), FT4 (9.01–19.04 pmol/l), TSH (0.35–4.94 μIU/ml), and TRAb (<1.5 u/l) (Table 1). This study was approved by the Institutional Ethics Review Board of Rui-jin hospital in Shanghai. All the participants were informed of the purpose of this study and gave informed consent.

The baseline anthropometric and clinical information, such as age, sex, smoking behavior, body weight and height, blood pressure, heart rate, etc., were all recorded. Blood was drawn after an overnight fast (≥8 h) and sera were stored at −80°C for future use.

Methods

Serum free T3 (FT3), free T4 (FT4), and TSH were measured by electro-chemiluminescence assay (Architect system, Abbott Laboratories, USA). The intra- and inter-assay coefficients of variation (CV), respectively, were 4.2 and 5.0% for FT3, 5.3 and 7.8% for FT4, and 5.0 and 5.3% for TSH. The test sensitivity for TSH was ≤0.01 μIU/ml. Serum TRAb levels were measured by ELISA (RSR Ltd. UK). The intra- and inter-assay CVs were 7.1 and 12.9%, respectively.

Serum ADMA concentrations were measured using ELISA (Alpco Diagnostics), with inter- and intra-assay variations less than 10%. Serum NT-proBNP levels were measured using a commercially available ELISA kit (Alpco Diagnostics, Biomedica Gruppee), with intra- and inter-assay variations of 6.5 and 4.4%, respectively.

Statistics

All the continuous data were given as the mean ± SEM. χ^2-test was employed to compare noncontinuous variables. Since ADMA was not normally distributed as determined by the Kolmogorov–Smirnoff test, non-parametric statistical tests were used for further analysis. The Mann–Whitney U-test and Kruskal–Wallis H-test were carried out to compare differences among ADMA, NT-proBNP, thyroid hormone levels, and other parameters between groups. The correlations between variables were investigated using Spearman's bivariate correlation test. Multiple regression analysis with ADMA as the dependent variable was performed to test the combined effect of independent factors on ADMA. Factors showing significant correlations with ADMA were included in multiple regression analysis. All statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL). A P value less than 0.05 denotes the presence of a significant difference.

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