Pro-A-type and N-terminal pro-B-type natriuretic peptides in different thyroid function states

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Summary

Questions under study: Natriuretic peptides are produced predominantly in the heart and secreted in response to volume expansion and pressure overload. A wide spectrum of cardiac changes is observed in thyroid dysfunctions. This study investigates mid regional pro A-type (proANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in different thyroid states and evaluates the effect of L-thyroxine treatment on natriuretic peptides in patients with subclinical hypothyroidism.

Methods: Case-control and double-blind, placebo-controlled trial. Sera from 161 female patients (35 with overt, 63 with subclinical hypothyroidism; 10 with overt, 14 with subclinical hyperthyroidism; 40 euthyroid controls) were analysed. ProANP and NT-proBNP were measured at baseline and 48 weeks after L-thyroxine treatment in subclinical hypothyroidism.

Results: Circulating proANP and NT-proBNP levels were higher in hyperthyroid patients than in hypothyroid and euthyroid patients ($p < 0.001$). Plasma proANP levels tended to be lower in overt hypothyroidism than in subclinical hypothyroidism. ProANP and NT-proBNP levels correlated weakly to thyroid stimulating hormone (TSH) ($r = -0.3$ and -0.2, respectively). The natriuretic peptide levels of subclinical and overt hypothyroid subjects showed no difference with those of euthyroid subjects. L-thyroxine treatment had no effect on natriuretic peptide levels in subclinical hypothyroidism.

Conclusion: Natriuretic peptide levels are altered in different thyroid states with a more pronounced effect in hyperthyroidism than in hypothyroidism. Hyperthyroidism should be considered in patients presenting with unclear symptoms and mildly elevated natriuretic peptide levels, as overt hyperthyroidism results in increased serum A- and B-type natriurectic peptide levels, typically seen in mild heart failure.

Key words: natriuretic peptides; hypothyroidism; hyperthyroidism

Introduction

A-type (ANP) and B-type natriuretic peptides (BNP) belong to the family of natriuretic peptides counterbalancing the renin-angiotensin-aldosterone system. ANP and BNP are produced in atrial and ventricular cardiomyocytes, respectively, and secreted in response to volume expansion or pressure overload, as seen primarily in congestive heart failure [1–5]. The use of natriuretic peptide levels has been shown to improve the management of patients with acute dyspnea [6].

The cardiovascular system is very sensitive to thyroid hormones, and a wide spectrum of cardiac changes occurs in overt thyroid dysfunction [7–9]. In subclinical thyroid dysfunctions similar but less pronounced cardiac changes are observed [10, 11]. In addition, thyroid hormones directly increase myocardial gene expression of natriuretic peptides [12]. Accordingly, previous studies have shown changes in natriuretic peptide levels in different thyroid function states [13–15].

ANP is the carboxy terminal part of a 126 aminoacid long prohormone (proANP). ANP and related precursor peptides comprise 98% of all natriuretic peptides in healthy subjects [16]. Mature

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peptides are bioactive and, thus, rapidly cleared from the circulation. N-terminal fragments of ANP and BNP are secreted together with the mature peptides but have longer half-lives than the biologically active peptides. Therefore they have been suggested to be more reliable analytes in clinical practice [17, 18]. However, results from various competitive immunoassays indicate that proANP can be subject to further fragmentation [4, 5]. Consequently, sandwich immunoassays for proANP might underestimate actual levels of proANP and immunoassays to mid regional proANP may be an advantage [19].

Accordingly, the present study evaluated NT-proBNP and mid regional proANP levels in a wide range of thyroid dysfunction, ie from overt hypothyroidism through subclinical states to overt hyperthyroidism. In patients with subclinical hypothyroidism, we evaluated natriuretic peptide levels before and after restoration of euthyroidism in a double-blind, placebo controlled study taking advantage from stored serum samples.

Patients and methods

We used stored samples of a wide range of patients with thyroid dysfunction. Reviewing the evolving literature regarding natriuretic peptide levels in thyroid dysfunction, we retrospectively analysed natriuretic peptide levels in thyroid dysfunction. The patients included in this study were examined and followed-up in the Thyroid Research Unit of the Division of Endocrinology, Department of Medicine at the University Hospital of Basel. After an overnight fast, all patients underwent full medical assessment and laboratory examinations to rule out non-thyroidal illnesses. Only women were included to exclude intersex variations. The exclusion criteria were as follows: clinically evident cardiovascular diseases, pituitary/hypothalamic disorders, or other nonthyroidal illnesses and obvious or suspected poor compliance.

The 161 subjects were selected as follows:

Study A

This study population was selected from a cohort of female patients followed prospectively in the endocrine outpatient clinic of the University Hospital of Basel. The patients had to be referred to the study from their general physicians or from the Division of Nuclear Medicine. To avoid a selection bias, all patients with available samples were included in this analysis. Collected sera from 35 women with overt hypothyroidism, 63 with subclinical hypothyroidism, 10 women with overt hyperthyroidism, 14 with subclinical hyperthyroidism and 40 euthyroid, age-matched female controls were analysed. Thyroid hormones, proANP and NT-BNP values in these patients were studied in the untreated state. All the control subjects were normal women – mainly staff members, their relatives, or friends. After an overnight fast, all the women underwent full medical assessment and laboratory examinations to rule out nonthyroidal illnesses. Overt hypothyroidism (n = 35; mean age 55.0 ± 12.1 years) was defined by a basal serum TSH >12 mU/L and decreased serum free thyroxine concentrations (<8 pmol/L). The underlying thyroid disorders consisted of autoimmune thyroiditis (n = 17), Graves' disease (n = 17, treated with radioiodine, surgery or carbimazole) and surgically resected goitre (n = 1). Subclinical hypothyroidism (n = 63), mean age 57.5 ± 9.8 years, was defined by a basal serum TSH concentration higher than 5.0 mIU/L in the presence of serum concentration of free thyroxine and triiodothyronine within respective reference ranges. The underlying thyroid disorders consisted of autoimmune thyroiditis (n = 33), Graves' disease (n = 20, treated with radioiodine, surgery or carbimazol), toxic multinodular goitre (n = 1, treated with radioiodine), surgically resected goitre (n = 5) and idiopathic subclinical hypothyroidism (n = 4). Overt hyperthyroidism (n = 10, mean age 54.5 [11.2] years) was defined by a basal serum TSH <0.1 mIU/L and increased serum free thyroxine concentrations (>22 pmol/L). The underlying thyroid disorders consisted of toxic adenoma (n = 5), Graves' disease (n = 2) and suppressive thyroid hormone treatment in thyroid cancer (n = 3). Subclinical hyperthyroidism (n = 14, mean age 50.9 [11.4] years) was defined by a basal serum TSH concentration lower than 0.1 mIU/L in the presence of serum concentrations of free thyroxine and triiodothyronine within the respective reference ranges. The underlying thyroid disorders consisted of suppressive thyroid hormone treatment due to goitre (n = 4) and thyroid cancer (n = 10). Euthyroid subjects (n = 40, mean age 50.6 [12.1] years) had serum concentrations of TSH, free thyroxine and triiodothyronine within normal reference ranges.

Study B

63 women with subclinical hypothyroidism were enrolled in a prospective, double-blind, placebo-controlled intervention trial to evaluate the effect of thyroid hormone treatment on lipid levels and symptom scores, as previously described [20]. Briefly, between September 1993 and May 1997, 66 ambulatory patients between 18 to 75 years old, with TSH levels more than 5.0 mIU/L on two consecutive blood tests, exaggerated TSH response after TRH stimulation, free T4 concentration within the normal range, and good general health were included. Exclusion criteria were coronary heart disease, pituitary/hypothalamic disorders, or other nonthyroidal illnesses; thyroid hormone medication up to three months before enrolment or an obvious or suspected poor compliance. Eligible patients were sequentially assigned to either the L-thyroxine treatment group (n = 33) or the placebo group (n = 33) according to a predefined randomisation list. The L-thyroxine dose was adapted continuously every 6 weeks to achieve optimal physiological hormone replacement. A total of 63 women completed the study according to the study protocol.

The studies were approved by the local Ethics Committee for Human Studies. All patients gave their written informed consent.

Hormone measurements and tests of peripheral hormone action

Serum samples were collected in the fasting state, immediately put on ice and processed within 30 minutes. Thereafter, they were kept frozen at –70 °C. Hormone measurements as well as mid regional proANP and NT-proBNP values were assessed at the initial diagnosis. Additionally, in all patients with subclinical hypothyroidism, mid regional proANP and NT-proBNP levels were assessed at the end of the treatment period after 48 weeks. Serum TSH concentration (reference range 0.3 to 4.0

mU/L) was measured by an immunometric assay (Delfia, Wallac, Turku, Finland). Free T4 (reference range 8.0 to 23.0 pmol/L) and total T3 (reference range 1.2 to 3.1 nmol/L) were determined by microparticel enzyme immunoassays IMx (Abbott, Diagnostic Division, Chicago, Ill., USA).

Mid regional proANP (amino acids 53 to 90) was detected in serum of all patients with a new sandwich immunoassay (B.R.A.H.M.S Seristra® LIA, B.R.A.H.M.S AG, Hennigsdorf, Germany) [19]. NT-proBNP levels were determined using the Elecsys NT-proBNP immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel). The analytic range extends from 20 to 35,000 ng/l. The total coefficient of variation was 3.3% at a level of 209 ng/l and 3.0% at a level of 7,431 ng/l [21].

Statistical analyses

All data are expressed as means with standard deviation (SD) in parentheses in text and tables and median, interquartile ranges and ranges in figures. Two group comparisons were performed by Student's t-test and by Mann-Whitney U test in nonparametric distribution, respectively. For multigroup comparisons, non-parametric Kruskal-Wallis ANOVA was applied with Dunnett's multiple group post-hoc comparisons. Treatment effects in the L-T4 or placebo group were analysed by paired Student's t-test or by Wilcoxon signed rank test in case of non-parametric distribution, respectively. Analysis of frequencies was performed with the use of contingency tables (chi-square with Bonferroni-correction for multiple comparisons).

P values <0.05 were considered statistically significant. Data were analysed using Statistica for Windows (version 5.0, StatSoft, Inc., Tulsa, OK). Figures were done with GraphPad Prism®, Version 4.00 for Windows (GraphPad Software, San Diego California, USA).

Results

Baseline characteristics

Clinical and biochemical characteristics of all study participants are summarised in table 1.

Euthyroid, subclinical and overt hypothyroid and hyperthyroid patients were well matched with respect to age. Characteristics of patients with subclinical hypothyroidism treated with L-T4 (n = 31) and placebo, respectively, (n = 32) before and after

Table 1

Characteristics of patients with various forms of thyroid dysfunction and of euthyroid controls.

Variable	Overt Hypothyroidism (n = 35)	Subclinical Hypothyroidism (n = 63)	Euthyroid (n = 40)	Subclinical Hyperthyroidism (n = 14)	Overt Hyperthyroidism (n = 10)
Age (yr)	55 (12) [51–59]	58 (10) [55–60]	51 (12) [47–55]	51 (11) [44–57]	55 (11) [47–63]
TSH (mIU/L)	45 (24) [37–53]	11 (6) [9–12]	1.7 (0.6) [1.5–2]	0.02 (0.01) [0.01–0.03]	<0.01 NA
Free thyroxine (pmol/L)	5 (2) [4–6]	12 (2) [11–12]	15 (3) [14–16]	20 (2) [19–22]	37 (9) [29–44]
Triiodthyronine (nmol/L)	1.2 (0.6) [1–1.4]	1.9 (0.4) [1.8–2]	1.7 (0.3) [1.5–1.8]	2.2 (0.4) [2.0–2.4]	3.6 (2.0) [2–5]
ProANP (pmol/L)	57 (32) [46–67]	71 (44) [60–82]	66 (31) [56–76]	82 (35) [62–103]	132 (60) [89–175]
NT-proBNP (ng/L)	67 (83) [37–96]	78 (72) [60–97]	71 (80) [46–97]	60 (43) [62–103]	204 (108) [89–175]

Data are shown as mean ± SD. Values in parentheses denote 95% CI. NA, not applicable.

Table 2

Parameters of women with subclinical hypothyroidism before and after L-T4 or placebo treatment.

Variable	before treatment	after 48 weeks	95% CI (of Δ mean)	p
Treatment with L-Thyroxine (n = 31)				
TSH (mU/L)	11.4 (6.6)	3.1 ± 1.7	5.8 to 10.9	<0.001
Free thyroxine (pmol/L)	11.3 (1.9)	17.4 ± 4.2	–8.6 to –5.1	<0.001
Triiodthyronine (nmol/l)	1.9 (0.5)	1.7 ± 0.1	0.1 to 0.4	<0.001
ProANP (pmol/L)	71.2 ± 47.8	68.3 ± 23.6	–12.7 to 22.8	ns
NT-proBNP (ng/L)	66.0 ± 48.5	80.3 ± 73.3	–37.6 to 8.9	ns
Treatment with Placebo (n = 32)				
TSH (mU/L)	10.1 (4.8)	9.9 ± 3.7	–1.2 to 1.3	ns
Free thyroxine (pmol/L)	11.9 (1.8)	12.5 ± 2.0	–1.4 to 0.2	ns
Triiodthyronine (nmol/L)	1.9 (0.3)	1.9 ± 0.1	–0.2 to 0.1	ns
ProANP (pmol/L)	71.1 ± 40.6	72.0 ± 29.1	–16.2 to 9.9	ns
NT-proBNP (ng/L)	90.4 ± 88.7	84.5 ± 75.3	–10.9 to 22.6	ns

Data are shown as mean (SD). Ns denotes not significant, CI denotes confidence interval

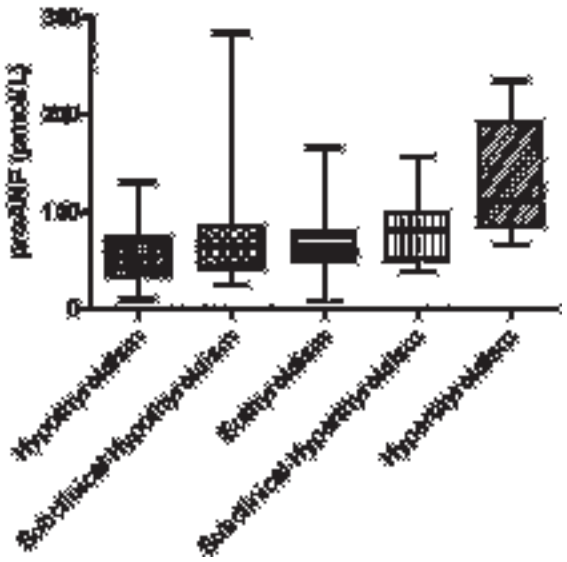

Figure 1

Pro-ANP levels in different thyroid dysfunction states compared to those in euthyroid controls. Lines denote median, boxes represent interquartile ranges and whiskers total ranges. For multigroup comparison, Kruskal-Wallis ANOVA with Dunnett's posthoc test was used.

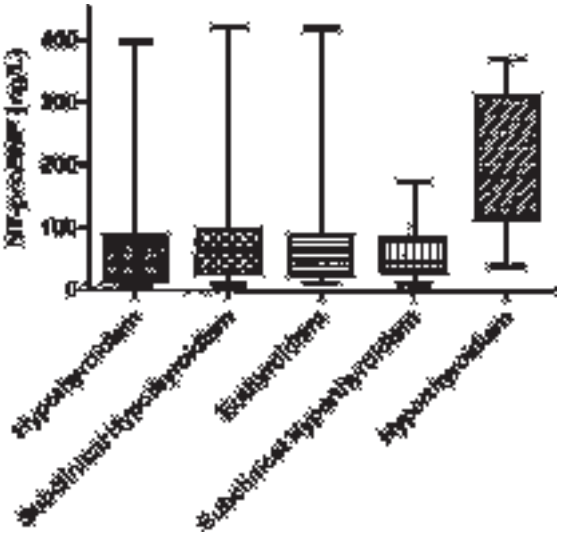

Figure 2

NT-proBNP levels in different thyroid dysfunction states compared to those in euthyroid controls. Lines denote median, boxes represent interquartile ranges and whiskers total ranges. For multigroup comparison, Kruskal-Wallis ANOVA with Dunnett's post-hoc test was used.

therapy are listed in table 2. At baseline, the two patient groups, T4-treated (n = 31) and placebo-treated (n = 32), were age-matched and well-balanced regarding serum thyroid hormone concentrations as well as mid regional proANP and NT-proBNP levels.

Natriuretic peptide levels

Mid regional proANP levels were significantly higher in overt hyperthyroidism than in any other group ($p < 0.001$). In subclinical hyperthyroidism, mid regional proANP levels were slightly lower compared to in overt hyperthyroidism and showed a trend to higher levels compared to in euthyroid patients. In overt hypothyroidism mid regional proANP levels were lower compared to those in subclinical hypothyroidism. There was no significant difference between mid regional proANP levels in subclinical and overt hypothyroid subject compared to in euthyroid subjects (figure 1).

Similarly to mid regional ProANP, NT-proBNP levels were higher in overt hyperthyroidism compared to in any other group ($p < 0.001$). However, there was no significant difference in NT-proBNP levels of euthyroid and overt hypothyroid, subclinical hypothyroid and subclinical hyperthyroid subjects (figure 2).

There was a significant correlation between proANP and NT-proBNP levels and TSH ($r = -0.30$, and $r = -0.21$, respectively) and fT4 ($r = 0.23$ and $r = 0.18$, respectively). Considering the subgroup of hyperthyroid subjects (subclinical and overt), the correlation of NT-proBNP levels and thyroid parameters was highly significant (TSH: $r = -0.51$; fT4: $r = 0.70$; T3: $r = 0.68$). In this subgroup, there was no significant correlation with proANP levels.

In female patients with subclinical hypothyroidism, L-T4 treatment had no effect on both, circulating mid regional proANP and NT-proBNP levels (table 2).

Discussion

In our patients, circulating natriuretic peptide levels are increased in hyperthyroidism. Using a novel assay, measurement of the mid regional ANP fragment shows subtle changes in subclinical thyroid dysfunction states, which are more pronounced than those of BNP.

Circulating natriuretic peptide levels correlate with thyroid function status, both in hyper- and hypothyroidism, reflecting myocardial and cardiovascular dysfunction [13–15]. In addition, thyroid hormones directly modulate ANP and BNP synthesis, as suggested by an increased cellular mRNA content, which was earlier shown in experimental studies [12, 22]. Thus, thyroid hormones may directly increase ANP levels independently of cardiac haemodynamics [13].

In our study in patients with overt hyperthyroidism, NT-proBNP levels increased by almost three fold compared to in euthyroid subjects. Mid regional ProANP levels showed only a two-fold increase. Conversely, the correlation of NT-proBNP levels, especially in hyperthyroid subjects, was stronger compared to the correlation of mid regional proANP levels. Thus, it is tempting to speculate that levels of NT-proBNP, with a predominant ventricular origin, reflect more accurately cardiac dysfunction in overt hyperthyroid patients, or direct thyroid hormone effects than mid regional proANP levels.

As a limitation of our study, cardiovascular dysfunction was only assessed clinically. Thereafter, no patient showed signs or symptoms of myocardial dysfunction exceeding NYHA I. Thus, severe, clinically apparent volume overload cannot

explain our results. Nevertheless, especially in overt hyperthyroidism the observed changes in natriuretic peptide levels might be influenced by mild, clinically unapparent volume overload only assessable by ultrasound or invasive examination. Indeed, heart failure or at least fluid overload can occur even in young hyperthyroid patients with no known heart disease and in the absence of atrial fibrillation [23]. Accordingly, values of natriuretic peptides in overt hyperthyroidism were of a comparable magnitude as seen in mild heart failure [17, 24].

Subclinical endogenous hyperthyroidism as well as treatment with suppressive doses of thyroxine has been reported to induce cardiovascular dysfunction [11, 25]. In subclinical hyperthyroidism, NT-proBNP levels were not significantly different compared to those in euthyroidism. In contrast, mid regional proANP levels tended to be increased compared to those in euthyroid subjects. This suggests that mid regional proANP, produced mainly in the atrium, better reflects cardiac adverse effects of mild hyperthyroidism. Thus, atrial derived natriuretic peptides seem to be a more subtle parameter than NT proBNP levels in indicating increased plasma volume in mild hyperthyroidism. However, this hypothesis should be verified in a much larger cohort of patients presenting with congestive heart failure with and without thyroid dysfunction.

Principally, changes in cardiovascular function which occur in patients with hypothyroidism are opposite to those of thyrotoxicosis [26]. Nevertheless, especially in the presence of preexisting cardiac disease, patients with overt hypothyroidism may present clinically with pleural effusion and congestive heart failure, also found in patients with thyrotoxicosis [27]. Even mild thyroid failure may disturb cardiac contractility and haemodynamics, changes that can be reversed by thyroxine replacement therapy [28, 29]. In this context, the absence of an increase of natriuretic peptides favours a direct effect of thyroid hormones on natriuretic peptide levels, in accordance with the experimental data [12, 22].

In our study, in contrast to a significant improvement regarding thyroid function, no effect of T4 substitution on natriuretic peptide levels was seen for patients with subclinical hypothyroidism. Our findings are, at least partially in contrast to recent reports [13, 15, 16]. Reasons for this discrepancy may include a suboptimal T4 treatment in some of our patients with subclinical hypothyroidism with a mean TSH level at the end of the study within the upper reference range. However, excluding these patients from the analysis did not alter the results. In the study by Schultz et al, the mean TSH level in patients with subclinical hypothyroidism before treatment was 17 mU/L with a decrease to 2 mU/L upon L-thyroxine treatment. This is in contrast to a less pronounced decrease of 11 mU/L to 3 mU/L in our study, which at least partially could explain the discrepant findings. Another reason could be that some comparisons in our study were underpowered. We had relatively small patient groups and did not perform a power calculation before the study was started.

In conclusion, natriuretic peptide levels are altered in different thyroid states with a more pronounced effect in hyperthyroidism compared to hypothyroidism. This seems to reflect distinct atrial and ventricular cardiac dysfunction in thyroid hormone excess or, alternatively, mirrors a direct effect of thyroid hormones on gene expression of natriuretic peptides. The prevalence of overt thyroid dysfunction is about 5% in the general population with an increasing prevalence in the elderly [30]. As overt hyperthyroidism results in slightly increased pro-ANP and NT-proBNP levels as typically seen in mild heart failure, hyperthyroidism should be considered in patients presenting with unclear symptoms and mildly elevated natriuretic peptide levels.

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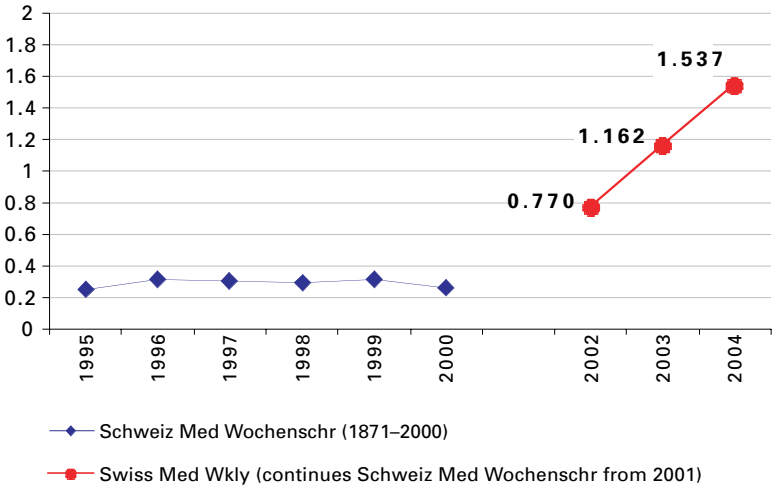

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