Arterial stiffness is increased in subjects with hypothyroidism

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Abstract

Background: The association between hypothyroidism and increased vascular resistance, arterial wall thickening and endothelial dysfunction is well recognized. The aim of the present study was to examine if hypothyroid subjects have increased arterial stiffness, a risk factor for cardiovascular morbidity and mortality.

Methods: Sixty-five subjects (59 females and 6 males) with normal thyroid function or hypothyroidism of varying degree were investigated by radial artery applanation tonometry and pulse wave analysis, for evaluation of arterial stiffness.

Results: Serum TSH values were positively correlated with central systolic blood pressure (r=0.258, p=0.037), central pulse pressure (r=0.316, p=0.010), augmentation pressure (r=0.299, p=0.015) and negatively with reflection time index (RTI), which indicates the pressure wave velocity (r=-0.311, p=0.012). Hypothyroid patients presented higher central systolic pressure and pulse pressure, higher augmentation pressure and lower RTI, indicating increased arterial stiffness in these subjects. RTI was independently related to age, central systolic pressure and TSH. Mild changes of arterial stiffness were observed even in subjects with TSH range 2.01–4.0 μU/ml suggesting that this group may have an early stage of mild thyroid failure.

Conclusions: Hypothyroidism, even in the subclinical stage, is associated with changes in arterial stiffness. The observed abnormalities in arterial stiffness may have detrimental effects on left ventricular function and coronary perfusion in hypothyroid subjects.

Keywords: Arterial stiffness; Hypothyroidism; Cardiovascular disease

1. Introduction

For many years, an association has been recognized between thyroid disease and the cardiovascular system. Especially hypothyroidism leads to abnormalities of the size and the function of the heart [1], increased vascular resistance [2] and greater arterial wall thickness [3]. We recently reported that patients with hypothyroidism present abnormalities in flow-mediated, endothelium-dependent vasodilatation of the brachial artery [4], whereas the capacity of the artery to dilate in response to nitrates is preserved; these abnormalities are compatible with endothelial dysfunction and impaired release of nitric oxide, an early step in the atherosclerotic process. Finally, recent epidemiological data [5] suggest that subclinical hypothyroidism is a strong indicator of risk for aortic atherosclerosis and myocardial infarction in elderly women.

Arterial stiffness appears to be an important risk factor for cardiovascular disease; changes in arterial wall elasticity may occur before and during the early stages of atherosclerosis, while increased arterial stiffness is an independent risk factor for cardiovascular morbidity and mortality [6–8]. Various techniques have been developed to assess arterial stiffness; radial artery applanation tonometry and pulse wave analysis is a non-invasive, reliable and reproducible technique providing information...
about systemic arterial stiffness [9–11], while other ultrasound techniques provide measurements of stiffness within a small arterial segment, which does not necessarily reflect the compliance of the arterial system as a whole [12,13].

Recently, Obuobie et al. [14] observed that patients with overt hypothyroidism (TSH>10 μU/ml) presented increased arterial stiffness, which was reversed following adequate thyroxine replacement. No data are available on milder subclinical forms of hypothyroidism, which are also associated with endothelial dysfunction [4] and increased risk for atherosclerosis [5]. Therefore, in the present study, we used pulse wave analysis in waveforms obtained from radial artery by applanation tonometry, to examine arterial stiffness in patients with recently diagnosed and untreated hypothyroidism of varying severity and compare the results with those obtained from subjects with normal thyroid function.

2. Subjects and methods

2.1. Population

Sixty-five subjects (59 women and 6 men, aged 44.4±13.5 years), who were referred for evaluation of suspected hypothyroidism, comprised the study population. No subject had evidence of atherosclerotic disease (based on clinical history, clinical examination and electrocardiogram), diabetes mellitus or renal failure. Subjects with clinical history of treated or untreated arterial hypertension were excluded from the study; none of the participants was receiving any medications. There were eight smokers who were equally divided in each group of our study. Each subject gave informed consent before entering the study and the local Scientific Committee approved the protocol.

2.2. Thyroid hormone measurements

Serum TSH, T3 and T4 levels were measured in all study participants within 1 week of the vascular studies. In subclinical hypothyroidism group, TSH values were confirmed on two chronically different occasions, separated by 2–3 months, and were accompanied by positive titers of thyroid autoantibodies and/or hypoechogenic pattern in thyroid ultrasound in all cases. Serum TSH was assayed by IRMA, Amerlex hs TSH coated Tube Assay (Ortho-Clinical Diagnostics, Amersham, UK, Johnson and Johnson Clinical Diagnostics) (intra- and interassay coefficients of variation 3.2% and 5.7%, respectively). Serum T3 and T4 levels were assayed by Amerlex-M T3 RIA kit and Amerlex-M T4 RIA kit, respectively (Johnson and Johnson Clinical Diagnostics). Normal range for T4 is 5.0–12.8 μg/dl for T3 0.5–1.75 ng/ml and for TSH 0.3–3.7 mU/ml.

2.3. Applanation tonometry and pulse wave analysis

In all studies, the SphygmoCor apparatus (ATCOR Medical, Sydney, Australia) was used; this system uses the principle of the pressure wave reflection from the periphery and their summation with the forward-going wave. Normally, the reflected wave arrives in the central arteries after closure of the aortic valve and does not influence central systolic pressure. However, in the presence of increased arterial stiffness, the increased pulse wave velocity of the stiffened arteries causes earlier wave reflection that reaches the heart in early systole. This increase in central systolic pressure due to wave reflection is referred to as augmentation and is an index of arterial stiffness.

Each subject was studied in the morning after a 10-min rest period. After blood pressure measurement, an arterial pressure waveform was recorded by planating the radial artery with a hand-held tonometer as previously described [9–11]. The tip of the tonometer contains a micromanometer that accurately records the pressure within the artery; pressure waveforms obtained by this method have been validated by comparing them with waveforms obtained by high fidelity transducer within the artery [15]. Data were collected directly into a portable microcomputer; after 20 sequential waveforms had been acquired, the integral software was used to generate an averaged peripheral and corresponding central waveform. Central aortic pressure waveforms were derived from the radial artery waveforms by using a transfer function; this method has been recently validated and shown to produce accurate transformation of the pressure wave, even under hemodynamic manipulation [16].

The following parameters were measured from the central aortic waveform: (1) augmentation pressure (AP: mm Hg), which is the difference between the second (reflected) and the first (primary) wave in mm Hg, (2) augmentation index (AI: %), which is the difference between the second and the first peaks of the central aortic waveform expressed as a percentage of the aortic pulse pressure, (3) central systolic, diastolic and mean pressures, (4) central pulse pressure, (5) time to the beginning of the reflected wave (t1: ms) and (6) reflection time index (RTI: %) which is the time to the beginning of the reflected wave expressed as a percentage of cardiac period (Fig. 1); this index is an estimate of the pulse wave velocity. The higher the augmentation pressure, augmentation index and pulse pressure, the higher is the arterial stiffness; the lower the time to the beginning of the reflected wave, the higher is the arterial stiffness.

2.4. Statistical analysis

Numeric values are expressed as mean±S.D. Linear regression and multiple regression (stepwise method) analysis were used to assess the relationship between
and LDL cholesterol, blood urea nitrogen, uric acid and blood glucose. Patients in group 4 were older and had higher peripheral systolic blood pressure, lower heart rate, higher triglycerides and tended to have higher total cholesterol. Characteristics of the four groups are shown in Table 1.

Serum TSH levels (log transformed) were significantly correlated to central systolic blood pressure \((r=0.258, p=0.037)\), central pulse pressure \((r=0.316, p=0.010)\), age \((r=0.405, p=0.001)\), cholesterol \((r=0.339, p=0.020)\), triglycerides \((r=0.336, p=0.027)\), heart rate \((r=-0.272, p=0.028)\), the reflection time index \((r=-0.311, p=0.016)\) and augmentation pressure \((r=0.299, p=0.015)\). No correlation was found between TSH and height, weight, body mass index, peripheral systolic, diastolic and mean pressure, central diastolic and mean blood pressure, augmentation index, HDL and LDL cholesterol, glucose, urea and uric acid.

Hemodynamic parameters for the four groups are given in Table 2. By analysis of variance, statistically significant differences were observed in peripheral systolic blood pressure \((F=3.27, p=0.027)\), central systolic blood pressure \((F=4.0, p=0.011)\), heart rate \((F=3.67, p=0.017)\), central pulse pressure \((F=3.17, p=0.03)\) and the following indices of arterial stiffness: augmentation pressure \((F=3.63, p=0.018)\), augmentation index \((F=2.8, p=0.047)\) and the reflection time index \((F=6.71, p=0.001)\).

RTI (log transformed) was significantly related to central systolic blood pressure \((r=-0.268, p=0.031)\), central pulse pressure \((r=-0.306, p=0.013)\), augmentation index \((r=-0.588, p<0.001)\), augmentation pressure \((r=-0.515, p<0.001)\), age \((r=-0.260, p=0.036)\) and TSH \((r=-0.311, p=0.012)\). To control for any effect of age, which is an important factor affecting arterial stiffness, multiple regression analysis was performed with RTI as dependent variable. Augmentation index, TSH and age were entered to the model as independent variables. It was showed that RTI was independently correlated to TSH \((p=0.012)\).

![Illustration of a central aortic pressure waveform. AP: augmentation pressure, the difference between the reflected and the primary wave, PP: pulse pressure, \(t_f\): time to the beginning of the reflected wave.](image-url)

### Table 1

Study groups characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N)</td>
<td>16</td>
<td>18</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Gender (females/males)</td>
<td>16/0</td>
<td>17/1</td>
<td>13/3</td>
<td>13/2</td>
</tr>
<tr>
<td>TSH range ((\mu)U/ml)</td>
<td>0.4–1.7</td>
<td>2.1–3.9</td>
<td>4.4–8.5</td>
<td>10.1–75.0</td>
</tr>
<tr>
<td>Age (years), ANOVA, (F=6.17, p=0.001)</td>
<td>37.6±9.9</td>
<td>42±13.9</td>
<td>43.4±13.9</td>
<td>55.5±11.2</td>
</tr>
<tr>
<td>TSH ((\mu)U/ml), ANOVA, (F=31.6, p&lt;0.001)</td>
<td>1.08±0.42</td>
<td>2.95±0.67</td>
<td>5.9±1.28</td>
<td>33.7±22.3</td>
</tr>
<tr>
<td>T4 ((\mu)g/dl), ANOVA, (F=19.6, p&lt;0.001)</td>
<td>8.6±1.6</td>
<td>9.2±1.7</td>
<td>7.2±1.2</td>
<td>4.7±2.3</td>
</tr>
<tr>
<td>T3 (ng/ml), ANOVA, (F=4.3, p=0.009)</td>
<td>1.1±0.18</td>
<td>1.35±0.33</td>
<td>1.16±0.38</td>
<td>0.87±0.54</td>
</tr>
<tr>
<td>Cholesterol (mg/dl), ANOVA, ns</td>
<td>205±51</td>
<td>226±51</td>
<td>213±46</td>
<td>268±90</td>
</tr>
<tr>
<td>Triglycerides (mg/dl), ANOVA, (F=3.35, p=0.031)</td>
<td>79±38</td>
<td>100±37</td>
<td>63±23</td>
<td>134±68</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl), ANOVA, ns</td>
<td>57±11.1</td>
<td>54.7±12</td>
<td>60.2±13</td>
<td>59±10.9</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl), ANOVA, ns</td>
<td>138.7±44.3</td>
<td>158.6±69</td>
<td>144.3±43.6</td>
<td>192±79</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), ANOVA, (F=3.27, p=0.027)</td>
<td>116.1±14.8</td>
<td>120.8±17.4</td>
<td>118.2±18.4</td>
<td>134±21.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg), ANOVA, ns</td>
<td>75.6±12.6</td>
<td>79.6±10.6</td>
<td>72.6±11.5</td>
<td>83.6±15</td>
</tr>
<tr>
<td>Glucose (mg/dl), ANOVA, ns</td>
<td>88.9±5.6</td>
<td>91.3±11</td>
<td>84.7±12.9</td>
<td>92.6±10.3</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl), ANOVA, ns</td>
<td>26.4±5.3</td>
<td>31.9±8.3</td>
<td>33.3±4.3</td>
<td>29.8±6.8</td>
</tr>
<tr>
<td>Uric acid (mg/dl), ANOVA, ns</td>
<td>3.3±0.9</td>
<td>4.0±0.69</td>
<td>4.1±1.1</td>
<td>3.5±1.6</td>
</tr>
</tbody>
</table>

ANOVA, degrees of freedom=3.
Subgroup analysis showed that arterial stiffness was statistically increased in group 2 (TSH=2–4 μU/ml) compared to group 1 (controls, TSH 0–2 μU/ml) as indicated by decreased RTI (p=0.001). Age, blood pressure and blood lipids were comparable between the two subgroups. On the other hand, mean RTI at group 2 was not significantly different from the respective RTI values of groups 3 (p=0.665) and 4 (p=0.99).

4. Discussion

The findings of the present study indicate that subjects with even mild forms of hypothyroidism present augmentation of the central arterial pressure by wave reflection, resulting from systemic arterial stiffening. These results suggest that hypothyroidism has detrimental effects on systemic arterial stiffness analogous to that of aging.

Applanation tonometry of the radial artery and pulse wave analysis used in the present study is a quick, noninvasive examination, with excellent reproducibility when used by trained observers and has been validated previously [11,17,18]. This method has been used before to describe changes of arterial stiffness in diabetes mellitus, hypertension and aging [19–21].

In the present study, subjects with hypothyroidism appear to present a lower RTI value reflecting the higher pulse wave velocity and arterial stiffness; it should be noticed that this change is independent of age and gender, which are well-known factors that affect arterial stiffness. Also other indices of arterial stiffness, like augmentation pressure and index, central pulse pressure and central systolic pressure, appear to be increased as well, suggesting a lower arterial compliance (increased stiffness) in these patients. Increased arterial stiffness in hypothyroid patients with TSH>10 μU/ml has been recently presented by Obuobie et al. [14]. The observed changes in arterial wall properties could be explained by various mechanisms: (1) endothelial function appears to be abnormal in patients with hypothyroidism [4] and it is known that elastic behavior of the arteries may be influenced by endothelium-derived relaxing factors [22]; therefore, the impaired endothelial function observed in hypothyroidism may lead to increased arterial stiffness and augmentation of the central aortic pressure. (2) Hypercholesterolemia, a frequent feature of hypothyroidism, is associated with increased arterial stiffness [23]; in our study, subjects with TSH>10 μU/ml tended to have higher cholesterol levels. (3) Hyperhomocysteinemia, which is frequently present in hypothyroid patients [24], may lead to endothelial dysfunction [25] and, subsequently, to decreased arterial distensibility [22]. (4) Finally, a direct effect of TSH on arterial wall cannot be excluded [26].

Abnormalities of the arterial wall have been previously described in hypothyroid patients. Using ultrasound measurements, Giannattasio et al. [3] reported that radial artery wall thickness was significantly and markedly greater in patients with a recent diagnosis of hypothyroidism; despite this increase in radial wall thickness, compliance at the same site was increased, a phenomenon not seen in the carotid artery. We should mention that the method used in our study examines the systemic arterial stiffness and not a local phenomenon as seen in the above mentioned report and that alterations in arterial function are not uniform throughout the arterial tree.

Both overt and subclinical hypothyroidism have been associated with cardiovascular disease. Silent myocardial ischemia is common in severe hypothyroidism [27], while low free-thyroxine levels are associated with carotid atherosclerosis [28]. Subclinical hypothyroidism has recently been shown to be a strong indicator of risk for aortic atherosclerosis and myocardial infarction in elderly women [5]. Lipid abnormalities, increased homocysteine, as well as a hypercoagulable state may account for this association between hypothyroidism and atherosclerotic disease [23,24,29,30]. The observed signs of increased arterial stiffness in the present study may be an early evidence of the atherosclerotic process in these patients, as they appear to occur before clinically apparent vascular disease. Recent data suggest that pulse pressure, a surrogate marker of arterial stiffness, is an independent predictor of cardiovascular risk in middle-aged and older subjects [6–8] and therefore our finding of increased pulse pressure in hypothyroid patients appears to be of interest, since it could be pathophysiologically linked to the increased risk of coronary heart disease in these subjects.

Subtle abnormalities in left ventricular systolic and diastolic function have been demonstrated in overt and subclinical hypothyroidism [31–34]. Arterial stiffening and
the resulting augmentation of the systolic aortic pressure adversely affects left ventricular performance and could contribute to the pathogenesis of left ventricular abnormalities observed in hypothyroid patients. In patients with arterial hypertension early return of the enhanced wave reflection may profoundly impair left ventricular relaxation function assessed by radionuclide angiography [35].

In our analysis of data, the group with high-normal TSH values (2.01–4.0 µU/ml) was considered separately. In these subjects, indices like augmentation pressure, augmentation index, pulse pressure and central aortic pressure did not differ compared to subjects with low-normal TSH values; however, RTI was markedly decreased in this group, suggesting that arterial stiffness was increased in these subjects. This is in accord with previous findings that these subjects with high-normal TSH values frequently develop hypothyroidism later in life [36], usually present hypercholesterolemia, which improves with thyroxine administration [37] and may have decreased endothelium-dependent vasodilatation, a sign of endothelial dysfunction [4]. More recently, it has also been suggested that an association between increasing TSH and LDL cholesterol becomes apparent in insulin resistant subjects with TSH values still in the normal range [38]. Together with the results presented here, it may be proposed that TSH values between 2.01 and 4.0 µU/ml are rather mildly abnormal and not high-normal and that the definition of the “normal” range for TSH values should probably be reconsidered.

In conclusion, patients with hypothyroidism present increased arterial stiffening leading to augmentation of the central aortic pressure with possible detrimental effects on left ventricular function and coronary perfusion. Until a specific treatment that can modify arterial stiffness is available, early treatment of hypothyroidism may be important in reducing the effects of this hemodynamic abnormality. The availability of a simple and accurate technique like applanation tonometry and pulse wave analysis will be of value in the early identification of the hemodynamic abnormalities and the evaluation of any interventions.

References


