Short term overt hypothyroidism induces discrete diastolic dysfunction in patients treated for differentiated thyroid carcinoma


Abstract

Background
Thyroid hormone has important effects on the cardiovascular system. The consequences of episodes of acute hypothyroidism on cardiac function have been investigated in only a few studies, and their results are inconclusive. Our objective was to investigate the effects of acute hypothyroidism on cardiac function in patients with iatrogenically induced subclinical hyperthyroidism after treatment for differentiated thyroid carcinoma.

Material and methods
Fourteen patients with a history of differentiated thyroid carcinoma on thyroid stimulating hormone (TSH)-suppressive thyroxine replacement therapy were studied. We assessed cardiac function before, and 1 and 4 weeks after withdrawal of thyroxine substitution. We measured serum levels of free thyroxin, triiodothyronine and TSH and used a new sophisticated Doppler echocardiography technique, tissue Doppler imaging (TDI), to assess detailed and quantitative assessment of systolic and diastolic cardiac function. Echocardiographic parameters in patients were compared to controls.

Results
Compared to controls, patients had higher left ventricular mass and wall thickness and decreased diastolic function during TSH-suppressive L-thyroxine substitution therapy. Thyroxine withdrawal resulted in a decrease in both early (E) and late (A) diastolic mitral inflow velocities, without impact on E/A ratio. Using TDI, late diastolic velocity (A′) decreased without impact on E′/A′ ratio. Left ventricular dimensions, wall thickness and mass did not change during thyroxine withdrawal.

Conclusions
Subclinical hyperthyroidism is accompanied by diastolic dysfunction. Subsequent acute hypothyroidism induces only subtle changes in diastolic function.
Introduction

Thyroid hormone has profound effects on the cardiovascular system. Hyperthyroidism induces cardiac arrhythmias, left ventricular (LV) hypertrophy and diastolic dysfunction, and enhances systolic function (1–3). Subclinical hyperthyroidism – i.e. suppressed thyroid-stimulating hormone (TSH) levels with normal free thyroxine (FT4) levels – is associated with increased heart rate and supraventricular arrhythmias, including atrial fibrillation, increased LV mass (LVM) with a slightly enhanced systolic function, and diastolic dysfunction. Diastolic dysfunction is at least partly reversible after restoration of euthyroidism and is associated with an increase in mortality (4–7). Conversely, hypothyroidism is associated with bradycardia, mild hypertension, increased peripheral cardiovascular resistance, heart failure (1,3,8,9), decreased cardiac output and diastolic dysfunction (1,3,10,11). Long-standing hypothyroidism can even result in asymmetrical septal hypertrophy (12) and pericardial effusion (6). Hypothyroidism is also associated with coronary artery disease, presumably because of associated hypercholesterolemia, hypertriglyceridemia and hypertension (1,3,13). Thyroxine substitution reverses most cardiovascular alterations associated with hypothyroidism (3,6,9,14).

Patients with differentiated thyroid carcinoma (DTC) are treated with total thyroidectomy and radioiodine ablative therapy, followed by long-term TSH-suppressive thyroxine replacement therapy (15–17). During the first period after diagnosis, patients are regularly withdrawn from thyroxine for TSH-stimulated thyroglobulin measurements and diagnostic 185-megabecquerel iodine-131 scintigraphy. The consequences of these episodes of acute hypothyroidism on cardiac function have been investigated in only a few studies up to now. However, the results of those studies have been inconclusive (18–27), varying from mainly decreased diastolic function (18,19,23,25,26), to mainly altered systolic function (21,24). In these studies, without control groups, these parameters were measured by different techniques (echocardiography, radionuclide imaging), without blinding the observers with regards to treatment modalities.

Therefore, we performed a prospective study in a homogeneous group of athyreotic DTC patients to assess the impact of overt hypothyroidism induced by short-term thyroxine withdrawal on cardiac function measured by a new sophisticated echocardiography technique: tissue Doppler imaging (TDI). This technique allows for detailed and quantitative assessment of cardiac parameters, including diastolic and systolic function (28,29). In addition, the researchers who collected and analyzed the echocardiographic data were blinded with regard to treatment modalities, and cardiac parameters of the patients were also compared to a matched group of controls who have no cardiovascular co-morbidities.
Subjects and Methods

Subjects
Patients were recruited from the outpatient clinic of the Department of Endocrinology of the Leiden University Medical Center. The Department of Endocrinology is a tertiary referral center for DTC. Patients included were those who had been diagnosed with DTC, had received initial therapy consisting of total thyroidectomy and radioiodine ablative treatment, and were planned for TSH stimulated iodine-131 whole body scanning for evaluation of the effect of prior radioiodine therapy or screening in case of positive thyroglobulin antibodies. The patients were on TSH-suppressive therapy, aiming at TSH levels below 0.1 mU/L (normal reference values for TSH 0.4–4.4 mU/L). No drugs known to influence cardiovascular parameters were allowed. None of the patients had hemodynamic instability, previous myocardial infarction, rheumatic fever, endocarditis, diabetes mellitus, or connective tissue disease. The study was approved by the local ethics committee and written informed consent was obtained from all subjects.

Study design
Fifteen DTC patients undergoing TSH-stimulated iodine-131 whole body scanning for follow-up were prospectively asked to participate in this study. On the last day of thyroxine therapy, on day 7 and on day 28 after withdrawal, hormonal and biochemical parameters were measured and echocardiography was performed. At each visit patients came to the outpatient clinic after an overnight fast and blood was collected for the measurement of TSH, FT4, triiodothyronine (T3) and creatinine concentrations. Height (m), weight (kg), resting blood pressure (mmHg) and heart rate (beats per minute) were documented. An independent cardiologist performed echocardiography at each visit.

Echocardiography: data acquisition
Echocardiography was performed with the patients in the left lateral decubitus position using a commercially available system (Vingmed System Vivid 7, General Electric/Vingmed, Milwaukee, WI, USA). Images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber, long axis) views. Standard two-dimensional and colour Doppler data, triggered to the QRS complex, were saved in Cineloop format. A minimum of three consecutive beats were acquired from each view and the images were stored for offline analysis (EchoPac 6.0.1, General Electric/Vingmed Ultrasound).

Left ventricular dimensions, fractional shortening and LV ejection fraction (LVEF) were measured from the M-mode recordings at the parasternal long-axis views (27).
LVM was calculated by the cube formula and using the correction formula proposed by Devereux et al. (31): $0.8 \times \{1.04[\text{LVEDD} + \text{PWT} + \text{IVST}]^3 - (\text{LVEDD})^3]\} + 0.6$, where, LVEDD is LV end-diastolic diameter, PWT is the posterior wall thickness, and IVST is interventricular septum thickness. LVM was corrected for body surface area to obtain LVM index (LVMI). LV hypertrophy was defined as LVMI > 120 g m² for men and > 116 g m² for women (31,32). Systolic function was evaluated by measurements of fractional shortening and LVEF (33).

The following parameters of diastolic function were measured: diastolic transmirtal peak velocities (E and A wave) and the E/A ratio, the isovolumetric relaxation time and the deceleration time of the E-wave. In addition, left atrium anteroposterior diameter was measured from the M-mode parasternal long-axis recordings. Quantitative diastolic data were derived from TDI data. For TDI data analysis, the digital Cineloops were analysed using commercial software (EchoPac 6.0.1, General Electric/Vingmed Ultrasound). The sample volume (4 mm³) was placed in the LV basal portions of the anterior, inferior, septal and lateral walls (using the 2- and 4-chamber images). The following parameters (mean values calculated from three consecutive beats) were derived: early diastolic velocity (E') and late diastolic velocity (A') and the E'/A' ratio.

Baseline echocardiographic parameters from patients were compared to a control group consisting of 24 individuals matched for age, gender, body surface area and LVEF. The controls were selected from an echocardiographic database containing this information and special care was taken to exclude those individuals with any cardiovascular co-morbidity. Those individuals referred for echocardiographic evaluation of known valvular disease, murmur, congestive heart failure, or cardiac transplantation evaluation were excluded. Accordingly, the controls comprised of patients with curable breast cancer referred for examination of cardiac function before they undergo adjuvant chemotherapy, and of patients experiencing non-ischemic chest pain, palpitations or syncope without murmur.

Acquisition of echocardiographic data was performed by one experienced observer, whereas data analysis was performed by a single independent observer, both blinded with regard to the study subgroups (patients and controls). Intra-observer reproducibility of quantitative M-mode measurements assessed by linear regression and Bland–Altman analysis showed an excellent agreement with high Pearson’s correlation coefficient ($r^2 = 0.99$) and small bias (0.1 ± 2.4 mm). Similarly, the intra-observer reproducibility of quantitative Doppler measurements was also excellent, with an $r^2$ value of 0.99 and small bias of 0.8 ± 3.6, with no significant trend for repeated measurements.

**Assays**

Serum FT4 concentration was measured with an IMx system (Abbott, Abbott Park, IL, USA) (intra-assay variability of 2.47–7.57% and interassay variability of 5.6–12.4%
at different levels). Serum TSH levels were determined with a Modular Analytics E-170 system (Roche Diagnostic Systems, Basel, Switzerland) (intra-assay variability of 0.88–10.66% and interassay variability of 0.91–12.05%). Serum T3 levels were measured by fluorescent polarization immunoassay using an Axsym system (Abbott) (intra-assay variability of 0.15–0.37% and interassay variability of 6.5–19%).

Statistical analysis
SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL, USA), was used to perform data analysis. Data are expressed as mean ± standard deviation, unless mentioned otherwise. Outcomes of patients at the three visits were compared using analysis of variance for repeated measures, and post-hoc analysis if appropriate. Data from healthy controls were compared to data from the patients using Kruskal–Wallis non-parametric tests. Differences were considered statistically significant at $P < 0.05$.

Results
Patient characteristics
Patient characteristics are detailed in Table 1. Fifteen patients were included in this study. One patient was excluded from the analysis because follow-up data were not obtained. Accordingly, 14 patients completed this study (3 men and 11 women), with a mean age of 51.6 ± 14.5 years. Median duration of TSH suppression was 1 year (range 0.5–44.6 years). The dose of thyroxine replacement before withdrawal was 162 ± 42 $\mu$g/ day. The control group consisted of 21 women and 3 men, with a mean age of 45.4 ± 8.5 years ($P = 0.16$ vs. patients).

Clinical and laboratory parameters
Thyroid hormone levels
Thyroid hormone levels are summarized in Table 2. At visit 1, serum FT4 concentrations were above the upper limit of the normal range (reference range, 10–24 pmol/L), TSH levels (reference range, 0.4–4.8 mU/L) were below normal range, and T3 levels (reference range, 1.1–3.6 nmol/L) were within normal range. Seven days after thyroxine withdrawal, FT4 levels were already slightly below the lower limit of the reference values, and TSH levels had increased significantly, whereas T3 levels were still within normal range. At visit 3, at the end of the study, all patients had elevated TSH levels and decreased FT4 and T3 levels (Table 2).
Weight and body mass index

Weight and body mass index were significantly different at visits 2 and 3 compared to visit 1, and were also different between visits 2 and 3 (Table 2).

Table 2: Weight, body mass index, blood pressure, heart rate and thyroid hormone parameters.

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Visit 1 subclinical hyperthyroidism</th>
<th>Visit 2 7 days withdrawal</th>
<th>Visit 3 28 days withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FT4 (pmol/l)</strong> (ref 10-24 pmol/l)</td>
<td>NA</td>
<td>26.4 ± 3.1</td>
<td>9.6 ± 1.9 *</td>
<td>2.2 ± 1.3 ††</td>
</tr>
<tr>
<td><strong>T3 (nmol/l)</strong> (ref 1.1-3.6 nmol/l)</td>
<td>NA</td>
<td>1.5 ± 0.5</td>
<td>1.1 ± 0.2 *</td>
<td>0.6 ± 0.2 ††</td>
</tr>
<tr>
<td><strong>TSH (mU/l)</strong> (ref 0.4-4.8 mU/l)</td>
<td>NA</td>
<td>0.3 ± 0.58</td>
<td>9.5 ± 15.5 *</td>
<td>105.2 ± 57.8 ††</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>72.5 ± 11.0</td>
<td>78.9 ± 18.5</td>
<td>79.9 ± 18.5 *</td>
<td>81.6 ± 18.5 ††</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>24.9 ± 3.1</td>
<td>26.5 ± 6.1</td>
<td>26.9 ± 5.9 †</td>
<td>27.6 ± 6.0 ††</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>124.8 ± 7.7</td>
<td>130.1 ± 23.2</td>
<td>130.2 ± 23.3</td>
<td>131.3 ± 20.1</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td>76.0 ± 6.9</td>
<td>81.7 ± 16.5</td>
<td>77.6 ± 12.9</td>
<td>85.5 ± 10.4 ‡§</td>
</tr>
<tr>
<td><strong>Mean blood pressure (mmHg)</strong></td>
<td>92.3 ± 6.3</td>
<td>97.8 ± 18.3</td>
<td>95.2 ± 15.4</td>
<td>100.8 ± 12.3</td>
</tr>
<tr>
<td><strong>Heart rate (BPM)</strong></td>
<td>70.4 ± 8.4</td>
<td>70.8 ± 8.0</td>
<td>65.2 ± 8.2 *</td>
<td>66.6 ± 6.7</td>
</tr>
</tbody>
</table>

Visit 2 reflects euthyroid to hypothyroid state, visit 3 reflects overt hypothyroidism. TSH= thyroid stimulating hormone, BMI= body mass index, BPM= beats per minute †= P< 0.05 compared to visit 1, ††= P≤ 0.001 compared to visit 1, †= P< 0.05 compared to visit 1, ††= P≤ 0.001 compared to visit 2, ‡= P< 0.05 compared to visit 2, §= P≤ 0.05 compared to controls.
Blood pressure and heart rate
At baseline, six patients had hypertension, but only one patient was on antihypertensive treatment. No differences were observed in systolic blood pressure and mean arterial pressure 7 and 28 days after l-thyroxine withdrawal. Diastolic blood pressure increased significantly at visit 3 compared to visit 2. Heart rate was significantly decreased at visit 2 (Table 2).

Echocardiography
LV dimensions and systolic function
At baseline, LVM, LVMI, IVST and PWT were significantly higher in patients with subclinical hyperthyroidism as compared to control subjects. However, none of the patients met the criteria for LV hypertrophy (31). Echocardiography showed no significant changes in M-mode measurements of LV dimensions and systolic function during acute withdrawal of thyroid hormone (Table 3).

Table 3: Left ventricular dimensions and systolic function

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Visit 1 subclinical hyperthyroidism</th>
<th>Visit 2 7 days withdrawal</th>
<th>Visit 3 28 days withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular mass (g)</td>
<td>135.6 ± 27.2</td>
<td>157.8 ± 31.2</td>
<td>163.9 ± 32.4 *</td>
<td>168.6 ± 42.4 *</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>73.6 ± 9.3</td>
<td>81.6 ± 12.1 *</td>
<td>84.1 ± 12.2 *</td>
<td>85.2 ± 16.7 *</td>
</tr>
<tr>
<td>Inter-ventricular septum thickness (mm)</td>
<td>8.3 ± 1.0</td>
<td>w9.9 ± 1.3 *</td>
<td>9.3 ± 1.4 *</td>
<td>9.5 ± 1.5 *</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>8.2 ± 0.7</td>
<td>9.5 ± 1.9 *</td>
<td>9.4 ± 1.2 *</td>
<td>9.7 ± 1.5 *</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (mm)</td>
<td>48.5 ± 4.5</td>
<td>46.9 ± 5.3</td>
<td>49.4 ± 5.0</td>
<td>48.9 ± 5.0</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (mm)</td>
<td>28.1 ± 4.1</td>
<td>28.7 ± 4.6</td>
<td>29.6 ± 3.5</td>
<td>29.1 ± 3.2</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>38.2 ± 3.4</td>
<td>38.4 ± 7.4</td>
<td>39.8 ± 5.7</td>
<td>40.1 ± 5.8</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>68.0 ± 4.2</td>
<td>68.0 ± 8.8</td>
<td>70.4 ± 6.1</td>
<td>70.3 ± 6.7</td>
</tr>
</tbody>
</table>

Visit 2 reflects euthyroid to hypothyroid state, visit 3 reflects overt hypothyroidism. * P< 0.05 compared to healthy controls

Diastolic function
Control subjects had significantly higher mean values for E- and E’-wave as compared to patients at baseline. The E’/A’ ratio -was higher in controls when compared to the patients’ baseline values. The values for A- and A’-wave were significantly lower in the patients at visit 3, 28 days after withdrawal, compared to visits 1 and 2. Baseline left atrium anteroposterior diameter was similar between patients and controls (Table 4). Twenty-eight days after withdrawal, E-wave was significantly lower compared to baseline. There were no changes in E/A ratio, E’/A’ ratio and left atrium anteroposterior diameter during the study (Table 4).
Discussion

The current study aimed at investigating the effects of overt acute hypothyroidism in DTC patients on cardiac function. At baseline, when patients were subclinically hypothyroid, patients had higher LV size and mass and decreased diastolic function as compared to controls. Thyroxine withdrawal resulted in an additional subtle decrease in both E- and A-wave velocities, without an impact on E/A ratio, indicating discrete unfavorable effects on diastolic function as assessed by echocardiography. In line with this observation, diastolic function, when more specifically analyzed by TDI, decreased. This was reflected in decreased late diastolic velocity (A’) without impacting E’/A’ ratio. Overt hypothyroidism increased diastolic blood pressure significantly, but had no effect on systolic blood pressure. Therefore, long-term subclinical hyperthyroidism is accompanied by diastolic dysfunction. Subsequent acute hypothyroidism induces subtle changes in diastolic function.

The impact of acute hypothyroidism on cardiac function has been investigated in only a few studies. These studies were inconclusive and mainly showed decreased diastolic function (18,19,23–25) or decreased systolic function (21,24), measured by different techniques (conventional echocardiography and radionuclide imaging). In addition, none of these studies compared their outcomes to a control group without cardiovascular comorbidities or had their observers blinded with regards to treatment modalities. Moreover, none of these studies measured cardiac function using TDI, a new and sophisticated technique that permits quantification of diastolic parameters which are independent of cardiac loading conditions (28,34,35).

Table 4: Diastolic function

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Visit 1 subclinical hyperthyroidism</th>
<th>Visit 2 7 days withdrawal</th>
<th>Visit 3 28 days withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (cm/sec)</td>
<td>68.8 ± 10.7</td>
<td>57.0 ± 19.2 *</td>
<td>55.6 ± 15.6 *</td>
<td>46.6 ± 15.1 **</td>
</tr>
<tr>
<td>A (cm/sec)</td>
<td>54.6 ± 12.0</td>
<td>50.6 ± 11.7</td>
<td>50.9 ± 9.9</td>
<td>40.6 ± 11.6 **</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.3 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>E’ (cm/sec)</td>
<td>-8.9 ± 1.6</td>
<td>-6.4 ± 2.6 *</td>
<td>-6.4 ± 2.4 *</td>
<td>-5.8 ± 1.6 *</td>
</tr>
<tr>
<td>A’ (cm/sec)</td>
<td>-6.5 ± 1.6</td>
<td>-6.9 ± 1.4</td>
<td>-6.8 ± 1.7</td>
<td>-5.7 ± 1.7 **</td>
</tr>
<tr>
<td>E’/A’ ratio</td>
<td>1.4 ± 0.5</td>
<td>1.0 ± 0.5 *</td>
<td>1.1 ± 0.7</td>
<td>1.2 ± 0.6 *</td>
</tr>
<tr>
<td>AP diameter of the LA (cm)</td>
<td>38.2 ± 4.1</td>
<td>37.2 ± 4.6</td>
<td>36.9 ± 5.1</td>
<td>36.1 ± 5.2</td>
</tr>
</tbody>
</table>

Visit 2 reflects euthyroid to hypothyroid state, visit 3 reflects overt hypothyroidism. E= peak flow of early filling phase, A= peak flow in atrial filling phase, E’= peak flow of early filling phase measured by Tissue Doppler Imaging, A’= peak flow in atrial filling phase measured by Tissue Doppler Imaging, LA= left atrium. *= P< 0.05 compared to healthy controls, †= P< 0.05 compared to visit 1, ‡= P< 0.05 compared to visit 2.
Our study is in line with only one other study that reported no impact on cardiac function after thyroxine withdrawal (20). In that study, conventional echocardiography without TDI was used and, in contrast to our study, the observers were not blinded with regards to treatment modalities.

After thyroxine withdrawal, early and late diastolic velocity (E and A, respectively) decreased mildly, whereas the E/A ratio was not affected. In addition, mean values for E, A and E/A ratio were still within the normal range of reference values when patients suffered from overt hypothyroidism (36). These findings imply that acute thyroxine withdrawal only minimally affects diastolic function.

In the present study, only six patients had an E/A ratio slightly below 1 during overt hypothyroidism. This is probably due to impaired ventricular relaxation associated with a delay in the energy-dependent reuptake of calcium by the sacroplasmatic reticulum, which in turn is under thyroid hormone control (26). This thyroid hormone control of cardiac function is mediated mainly by T3 (3), which in our study declined significantly during thyroxine withdrawal. Although the findings of the present study suggest minimal unfavorable cardiovascular effects of thyroxine withdrawal, the potential negative cardiovascular consequences of thyroxine withdrawal before diagnostic iodine-131 whole body scanning could be clinically relevant, especially in patients at cardiovascular risk (1,37,38). Therefore, recombinant TSH stimulation might be an attractive alternative in ‘low-risk thyroid carcinoma patients’ and/or high-risk cardiovascular patients.

At baseline, when patients had subclinical hyperthyroidism, echocardiography revealed decreased diastolic function. This is in line with a previous study in patients with exogenous subclinical hyperthyroidism (5). The clinical consequences of isolated diastolic dysfunction in subclinical hyperthyroidism are not entirely clear, but could be accompanied by increased morbidity and mortality when compared to isolated diastolic dysfunction in other conditions, especially in long-term subclinical hyperthyroidism (39). It has been suggested that diastolic dysfunction in subclinical hyperthyroidism results from an increased LVM (40,41). In our study, however, no patient fulfilled the criteria for LV hypertrophy, although there was a significant elevation in LVM at baseline compared to controls. Therefore, biochemical effects of thyroid hormone on cardiac function instead of increased LVM are more likely involved in the induction of diastolic dysfunction (1). Nonetheless, additional studies with longer follow-up are needed to elucidate the effects on LV dimensions and mass.

Systolic blood pressure did not change after thyroxine withdrawal, whereas diastolic blood pressure was higher at visit 3, when patients were overtly hypothyroid compared to visit 2, when patients were mildly hypothyroid. These findings are in line with those of previous studies (3, 10, 19, 42, 43). The increase in diastolic blood pressure in hypothyroidism is ascribed to increased peripheral vascular resistance (3, 43).
In conclusion, in the present study we demonstrated that long-term iatrogenically induced subclinical hyperthyroidism in patients with DTC induces diastolic dysfunction. Subsequently, overt acute hypothyroidism induces discrete decreases in diastolic parameters.
References

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