

# Impact of Therapy with L-Thyroxine on the Evolution of Arterial and Aortic Stiffness in Female Patients with Overt and Subclinical Hypothyroidism

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*The objective of this study is to highlight the impact of therapy with L-thyroxine on the altered arterial stiffness (AS) and reduced aortic distensibility (AoD), as well as on the left ventricular (LV) hypertrophy (LVH) and diastolic dysfunction (DD) in hypothyroid female patients.*

**Keywords:** thyroid stimulating hormone, free thyroxine, arterial stiffness, aortic elasticity, left ventricular hypertrophy, diastolic dysfunction

In physiological condition, thyroid hormones exert on the heart and vessels several genomic and nongenomic mediated effects. The active form, triiodothyronine ( $T_3$ ), increases the cardiac inotropism and chronotropism and induces vasodilatation in the periphery determining the reduction of the systemic vascular resistance (SVR) [1]. In thyroid hormone deficiency, especially of  $T_3$ , occurs the elevation of SVR, leading to systemic hypertension, followed by left ventricular (LV) hypertrophy (LVH) and diastolic dysfunction (DD) [2, 3]. On the other hand, hypothyroidism favours the occurrence of precocious and accelerated atherosclerosis, initiating degenerative processes in the arterial walls followed by the impairment of the elastic responsiveness of arterial walls, designated as arterial stiffness (AS) [4-6], and by the reduction of the elastic resistance opposed by the aorta against its distension, named aortic stiffness [7-9].

The fact that increased AS and reduced aortic distensibility (AoD) were detected even in subclinical hypothyroidism, is a subject of debate in many studies [7, 8].

All these parameters can be assessed non-invasively by various techniques. AS can be determined by pulse wave velocity (PWV) which is inversely associated with the vascular compliance [6]. PWV is the most well-validated method, with high accuracy, reproducibility and correlated with cardiovascular (CV) outcomes [10-12]. On the other hand, echocardiography offers the possibility to measure aortic diameters, to calculate several parameters that characterise aortic elasticity, LV mass index (LVMI) defining LVH and to accurately identify DD [13-15].

It remains the question if the substitution therapy with L-thyroxine could reverse those changes? There are data that describe a progressive improvement of AS and of AoD and the reduction of LVH and DD after the beginning of substitution therapy, which can be attributed to the beneficial effect exerted by L-thyroxine on the CV system [16].

The aim of this study is to assess, by means of echocardiography, the prevalence of AS and of impaired aortic elasticity in female patients with overt and subclinical hypothyroidism in comparison with age-matched healthy controls as well as their relationship with the gravity of the thyroid dysfunction, defined by levels of thyroid stimulating hormone (TSH) and  $FT_4$ . Another purpose is to evidence if

these alterations are reversible under therapy with L-thyroxine.

## Experimental part

Our study was conducted on 122 hypothyroid women without cardiovascular diseases or risk factors for atherosclerosis and 31 controls, divided into three groups: group A-81 patients with overt hypothyroidism, B-41 with subclinical disease and C-31 healthy age-matched controls. We assessed AS by measuring pulse wave velocity (PWV). We determined echocardiographically the indexes characterising the aortic elasticity: aortic strain (AoS), aortic stiffness index (AoSI), AoD and have calculated LV mass index (LVMI), E/A and E/e' ratio.

## Material and method

From all hypothyroid patients admitted in the Clinic of Endocrinology of our hospital between 2015 - 2018, we selected a group of 121 hypothyroid women who were still untreated with L-thyroxine. Taking into account that age, obesity and high blood pressure (BP) are well-known predictors of AS and DD, we excluded all subjects aged over fifty-four years, with body mass index (BMI) over 30, or with BP over 139/89 mmHg. We excluded all participants with diabetes mellitus, overt CV diseases or chronic renal diseases, dyslipidaemia (low density lipoprotein (LDL) cholesterol over 135 mg/dL), women who were postmenopausal or had history of smoking that could explain the presence of subclinical atherosclerosis [17,18]. We followed the evolution of these patients under therapy with L-thyroxine and evaluated AS, the aortic elasticity, LVH and DD initially and after 6 months of therapy when all patients reached the euthyroid state.

**Study groups:** for practical reasons, considering the severity of the thyroid disease, expressed by levels of TSH and  $FT_4$ , we divided our patients in three subgroups:

- group A: eighty-one patients with overt hypothyroidism;
- group B: forty-one subjects with subclinical disease.
- group C: thirty-one healthy, age matched, premenopausal women, with similar characteristics as our patients served as a control group used to compare our results.

**Thyroid evaluation:** the diagnosis of hypothyroidism was confirmed by increased levels of TSH (over 4.67 mIU/L). Subclinical hypothyroidism was established on the

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increased levels of TSH and normal values of free  $T_4$  (FT<sub>4</sub>). Overt hypothyroidism was diagnosed by high levels of serum TSH and low levels of FT<sub>4</sub>. Serum TSH, FT<sub>4</sub> and FT<sub>3</sub> were measured by chemiluminescent microparticle immunoassay (CMIA), with the following normal values: TSH 0.465-4.67 mIU/L, FT<sub>4</sub> 0.71-1.85 ng/mL (9.13-23.81 pmol/L), and FT<sub>3</sub> 1.71-3.71 ng/mL (2.65-5.69 pmol/L). Antithyroid antibodies (anti peroxidase-TPO, respectively antithyroglobulin) were determined by ELISA (Enzyme Linked Immunosorbent Assay), normal range being considered below 60 IU/L. Thyroid ultrasound was performed using Siemens system, with a linear transducer (5.0-14 MHz).

**Cardiological evaluation:** after a rigorous clinical exam and assessment of systolic (SBP) and diastolic blood pressure (DBP), PWV was determined at the level of the right carotid and then, of the right femoral artery, with an SphygmoCor device, software version 9. PWV was calculated by measuring the time needed for the arterial waveform to travel between 2 sites along a vascular segment. The obtained values were compared by the system with the population reference range values.

The dimensions and function of cardiac cavities, LV mass index (LVMI) were evaluated using a Siemens echocardiograph, according to guidelines recommendations [19], by the same skilled operator to avoid inter-observer differences.

In order to assess the aortic elasticity, systolic ( $S_0$ ) and diastolic diameters ( $D_0$ ) were measured in M-mode at a level of 3-4 cm above the aortic valve, from a transthoracic parasternal long-axis view, at the time of maximum aortic anterior motion, and at the peak of the QRS complex, respectively. Several parameters were calculated:

- Aortic strain (AoS) =  $(S_0 - D_0) / D_0$ ;
- Aortic stiffness index  $\beta$  (AoSI) =  $\ln(SBP/DBP) / \text{strain}$ , where 'ln' means natural logarithm;
- Aortic distensibility (AoD) =  $(2 \times \text{strain}) / (SBP - DBP)$ .

To assess the presence of DD, we recorded in pulsed Doppler the mitral inflow and analysed the peak early diastolic velocity (E), the late diastolic velocity (A), the E/A ratio, and the isovolumetric relaxation time (IVRT) in apical 4-chamber view at the level of mitral valve annulus. Tissue Doppler (TDI) was used to record mitral annulus early diastolic velocity (e') and late diastolic velocity at septal and lateral mitral annulus and E/e' ratio was calculated, values over 14 strongly suggesting DD. DD was diagnosed according to guidelines recommendations [19].

**Data analysis** was performed using SPSS v.25 .0 (Statistical Package for the Social Sciences, Chicago, IL, USA). Continuous variables were presented as a mean and standard deviation (SD) or median and associated quartiles (Q1-25 percentage quartile, Q3-75 percentage quartile) and categorical data were presented as counts (percentages). We performed descriptive and inferential statistics analysis to summarize the characteristics of the study population. To evaluate the proportion of diastolic dysfunction in groups, we applied the chi-squared test ( $\chi^2$ ). The results of the Shapiro-Wilk normality test showed a non-Gaussian distribution, which is why we continued to use nonparametric tests. For comparing the three groups (A, B, C) we used the Kruskal-Wallis H test followed by a post-hoc analysis with Mann-Whitney U test with Bonferroni correction applied. Wilcoxon signed-rank test was used to appreciate the evolution of PWV, AoD, AoS and AoSI after 6 months of therapy. A p value of less than 0.05 was considered to indicate a statistically significance. The study was approved by the Ethics Committee of our hospital and all patients signed a written consent.

## Results and discussions

We documented in all patients impaired AS, AoS, AoSI and AoD and increased prevalence of LVH and DD, correlated with the severity of thyroid dysfunction, expressed by thyroid stimulating hormone (TSH) and free thyroxine (FT<sub>4</sub>) levels. We emphasized strong correlations between AS, AoS, AoSI, AoD, LVMI and E/e' ratio and levels of TSH for both groups ( $p < 0.0001$ ) and with FT<sub>4</sub> for overt forms ( $p < 0.0001$ ). We evidenced a significant regression for all those parameters after 6 months of substitution therapy with L-thyroxine.

One of the earliest consequences of hypothyroidism is subclinical atherosclerosis which precipitates the occurrence of other CV complications. In this study, conducted on 122 premenopausal female patients, newly diagnosed with overt or subclinical hypothyroidism, without CV diseases or risk factors, we tried to evidence the increased prevalence of AS and of the impaired aortic elasticity as well as their association with LVH and DD in comparison with 31 age matched healthy female controls. The results regarding clinical characteristics and laboratory data for all three groups are presented in table 1. All measurements were repeated in both patient groups after 6 months of therapy with L-thyroxine when all patients regained the euthyroid state.

All patients with overt hypothyroidism had PWV values significantly higher than those determined in controls ( $p < 0.001$ ) and the ones measured in group B ( $p = 0.003$ ), (table 1).

86.41% of group A and 53.65% of group B had altered AS, defined by pathological values of PWV of over 9 m/s, (fig. 1). PWV values were significantly correlated with levels of TSH and FT<sub>4</sub> in patients with overt hypothyroidism and only with TSH in those with subclinical disease (table 2). The impairment of aortic elasticity, characterised by indexes like AoS, AoSI and AoD, detected noninvasively, by means of echocardiography, was a common finding in our patients, but not in controls (fig. 1). All these indexes were significantly correlated with the levels of TSH and FT<sub>4</sub> in group A and only with TSH in group B, (table 2).

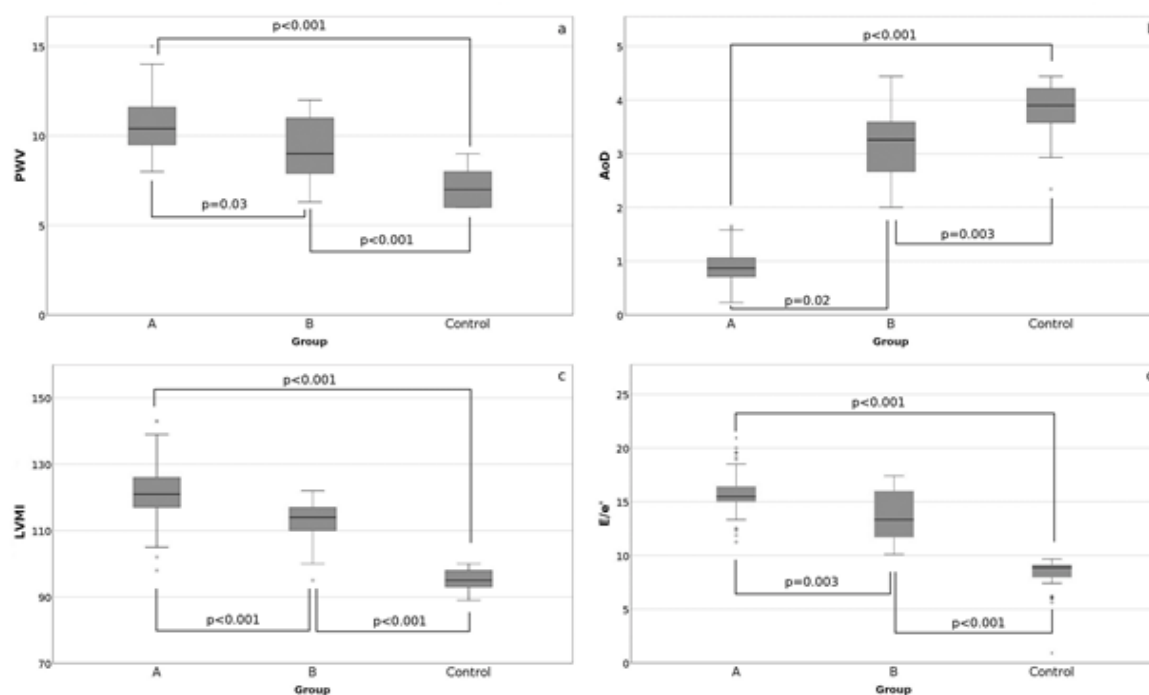
These indexes were significantly correlated with PWV levels ( $p < 0.001$ ). We repeated the assessment of PWV and of the indexes characterising aortic elasticity after 6 months of therapy with L-thyroxine and noticed a significant improvement of these parameters in group A and in a lesser extent in group B associated with the normalisation of thyroid hormones (fig. 2).

The incidence, magnitude and significance of impaired AS was debated in many studies. In their papers Biondi, Kilic et al and Lu Ming et al [6,20,21], debated the mechanisms responsible for the altered AS, its occurrence even in subclinical hypothyroidism and the most suitable methods for its assessment. The hypothesis that the elevated PWV correlates with increased LV afterload, being incriminated in the development of LVH and DD was discussed by other authors [5,20,22]. Masaki et al. [5] debated over AS's diagnosis in patients with subclinical disease and the implication of altered AS in the development of DD. Other authors [16] discussed the reversibility of endothelial dysfunction and AS under therapy with L-thyroxine. Many studies debated over the predictive value of AS parameters, independent of age, race and blood pressure values in patients with hypothyroidism, even in subclinical forms [10,12]. AS, measured by PWV either in the aorta or peripheral arteries, has emerged as a surrogate marker of atherosclerosis and an independent predictor of CV events [10]. The importance of altered aortic elasticity was debated in fewer studies like the one conducted by

**Table 1**  
CLINICAL CHARACTERISTICS AND RESULTS OF LABORATORY DETERMINATIONS IN STUDY GROUPS

Results of clinical, laboratory and echocardiographic parameters	Group A 81 patients	Group B 41 patients	Group C 31 controls	P		
				A-B	B-C	C-A
Mean age (years)	51 (47-53)	49 (47-53.5)	49 (45-53)	0.652	0.405	0.370
Body Mass Index (kg/m <sup>2</sup> )	27.1 (26.6-28)	26.6 (25.9-27.5)	26.4 (25.6-27.2)	0.009*	1	0.001*
Systolic Blood Pressure (mmHg)	130 (120-139)	130 (120-134)	125 (120-130)	0.169	0.413	0.002*
Diastolic Blood Pressure (mmHg)	85 (80-89)	80 (70-81.5)	70 (70-75)	<0.0001*	0.237	<0.0001*
TSH (0.465-4.67 mIU/L)	54 (43.75-64.5)	12.3 (9.74-15.6)	1.1 (1-1.4)	<0.0001*	0.002*	<0.0001*
FT <sub>4</sub> (9.13-23.81 pmol/L)	5.7 (4.9-6.8)	12 (10.9-15)	13.2 (12.9-13.6)	<0.0001*	1	<0.0001*
LDL cholesterol (mg/dl)	130 (126-135)	114 (110.5-117)	100 (100-106)	<0.0001*	0.003*	<0.0001*
Pulse Wave Velocity (m/sec)	10.4 (9.45-11.6)	9 (7.85-11)	7 (6-7)	0.003*	<0.0001*	<0.0001*
Aortic strain (%)	6 (5-7.14)	8.27 (7.16-9.31)	10 (9.28-10.71)	<0.0001*	0.001*	<0.0001*
Aortic stiffness index $\beta$	7.42 (6.15-8.97)	6.21 (5.65-7.51)	5.16 (4.97-6)	0.063	0.001*	<0.0001*
Aortic distensibility (10mmHg)	2.46 (2.09-3.1)	3.25 (2.64-3.65)	3.89 (3.57-4.28)	<0.0001*	0.113	<0.0001*
LVM Index (g/m <sup>2</sup> )	121 (117-126)	114 (110-117)	95 (93-98)	<0.0001*	<0.0001*	<0.0001*
E/A ratio	0.75 (0.54-1)	1.05 (0.96-1.28)	1.27 (1.21-1.43)	<0.0001*	0.026*	<0.0001*
E/e' ratio	15.48 (15-16.58)	13.33 (11.67-16)	8.88 (7.41-9.17)	<0.0001*	<0.0001*	<0.0001*
IVRT (msec)	107 (100.5-117)	97 (94-100)	95 (93-96)	<0.0001*	0.409	<0.0001*

Legend: TSH=thyroid stimulating hormone; FT<sub>4</sub>=free thyroxine; FT<sub>3</sub>=free triiodothyronine, LDL= low-density-lipoprotein; LVM=left ventricular mass index; IVRT=isovolumetric relaxation time. Values are presented as median (Q<sub>1</sub>-Q<sub>3</sub>). Kruskal-Wallis H test followed by a post-hoc analysis with Mann-Whitney U test. \*significance threshold value reached (adjusted significance values by Bonferoni correction).



Legend: PWV=pulse wave velocity, AoD=aortic distensibility, LVM=left ventricle mass index. Kruskal Wallis H test followed by U-Mann Whitney test with Bonferroni correction applied of PWV(a), AoD (b), LVM (c) and E/e' (d)

Fig. 1. Prevalence of arterial stiffness, impaired AoD, LVH and DD in study groups

**Table 2**  
CORRELATIONS BETWEEN THE SEVERITY OF HYPOTHYROIDISM, EXPRESSED BY LEVELS OF TSH AND PARAMETERS CHARACTERIZING AS, AORTIC ELASTICITY, LVH AND DD

Parameter	Group A			Group B		
	r	CI	p	r	CI	p
PWV	0.856	0.785;0.905	p<0.001	0.986	0.974;0.992	p<0.001
AoS	-0.785	-0.698;-0.802	p<0.001	-0.873	-0.799;-0.911	p<0.001
AoSI	0.767	0.683;0.813	p<0.001	0.686	0.621;0.719	p<0.001
AoD	-0.783	-0.691;-0.823	p<0.001	-0.834	-0.785;-0.897	p<0.001
LVMi	0.786	0.686;0.857	p<0.001	0.91	0.777;0.931	p<0.001
E/e'	0.887	0.786;0.943	p<0.001	0.787	0.596;0.896	p<0.001

Tarim et al on 38 subjects with subclinical hypo-thyroidism [7]. The importance of this dysfunction in patients with subclinical hypothyroidism was also discussed in other articles [8,16]. Other authors [9] debated over the predictive value of reduced aortic elasticity for the assessment of cardiovascular risk.

LV hypertrophy was detected in the majority of our patients, both with overt and subclinical hypothyroidism, but in the latter group LVMI values were lower (p<0.001), figure 1. LVH was significantly correlated with the levels of thyroid hormones, table 2, but also with PWV and with all parameters characterising the aortic elasticity. We noticed a slight, but significant regression of LVH after 6 months of therapy with L-thyroxine (p<0.001).

The development of a mild to moderate LVH during the evolution of overt hypothyroidism is a well-established entity [1,20,23]. Some studies over LVH in hypothyroidism, performed by means of magnetic resonance imaging, revealed structural changes in the myocardium, confirmed

by histological studies. Considering LVH as a negative predictor for future adverse cardiac events [15,22], its prevention, by thyroid hormone therapy, may be associated with better outcomes on cardiovascular events.

We determined an increased prevalence of DD in both patient groups: 82.7% in group A, and 39.22% in patients with subclinical hypothyroidism (fig. 1). We documented in both groups significant correlations between E/e' ratio and TSH and FT<sub>4</sub> levels (table 2), but also with PWV, AoS, AoSI, AoD and LVMi were also documented. After 6 months of therapy with L-thyroxine we documented an improvement of DD.

In several articles, regarding the diagnosis of DD in hypothyroidism [13-15], by using pulsed and TDI Doppler, significant abnormalities of LV relaxation, with prolongation of deceleration time and of IVRT and reduction of E/A ratio were demonstrated. By both methods, the authors demonstrated a wide spectrum of significant abnormalities of DD, but TDI was more sensible. It is known that overt

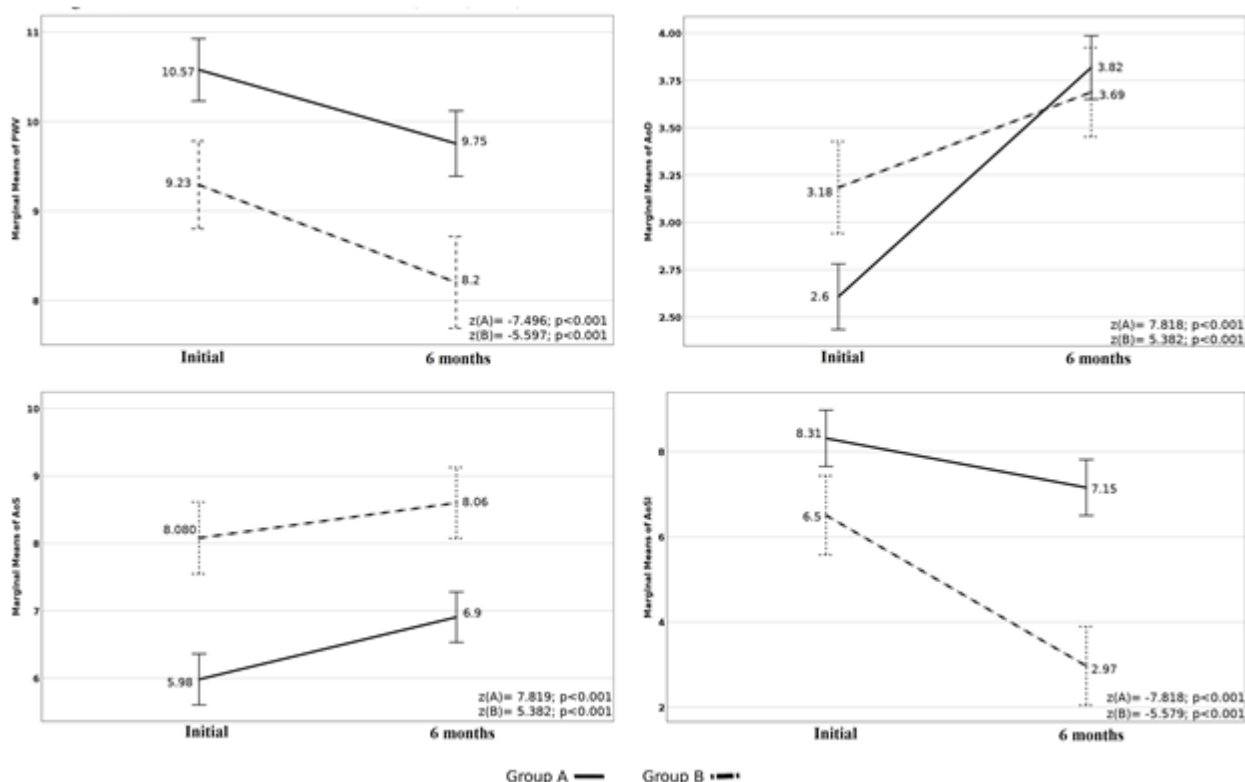


Fig. 2. Six months evolution of PWV, AoD, AoS, AoSI

and subclinical hypothyroidism can lead to diastolic or even systolic heart failure [22]. The diagnosis may be difficult and the symptoms are insidious and often confused with those of the underlying disease. The echocardiographic evaluation, using pulsed Doppler, can fail the diagnosis, requiring subtler techniques like TDI, strain and strain rate. Many authors have shown that hypothyroidism, even in subclinical form, is commonly associated with LVH and DD which could be reversible under treatment with thyroid hormones [16].

In hypothyroidism AS, reduced aortic distensibility, increased LVMI and DD are linked together having the same pathophysiological backgrounds. AS precedes the development of LVH and DD and its precocious assessment and therapy can prevent the evolution to heart failure. Therefore, in hypothyroid patients with altered AS, it is justifiable to perform a detailed echocardiographic exam to identify LVH and DD in order to initiate an adequate substitution therapy as soon as possible.

### Conclusions

Altered AS, reduced aortic elasticity, LVH and of DD were common findings in patients with overt hypothyroidism, but also in those with subclinical disease. These alterations were significantly correlated with the severity of hypothyroidism, expressed by the levels of thyroid hormones and denoted a significant tendency to regression under therapy with L-thyroxine.

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