



# Studies on Serum T<sub>3</sub>, T<sub>4</sub>, TSH, Progesterone and Oestrogen in Cardiovascular Disease Patients

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## Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

## Article Information

DOI: 10.9734/IJBCRR/2024/v33i2856

## Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/110973>

Original Research Article

Received: 09/12/2023  
Accepted: 14/01/2024  
Published: 15/02/2024

## ABSTRACT

**Aim:** This research was done to ascertain if thyroid hormones and female sex hormones (progesterone and estrogen) play a role or are a risk factor in the development of cardiovascular diseases.

**Study Design:** This is an observational study, specifically a case-control study.

**Place and Duration of Study:** This study was conducted at Enugu State University Teaching Hospital for six months.

**Methodology:** Blood samples were collected from 20 persons with cardiovascular disease. The sera from the study subjects were estimated for T<sub>3</sub>, T<sub>4</sub>, and TSH using the ELISA technique. The

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same parameters were estimated in 20 healthy individuals, and the results from both groups were analysed using SPSS version 21.

**Results:** There were no significant differences in serum T3, T4 and TSH, Progesterone and Estradiol ( $p=0.236$ ,  $p=0.834$ ,  $p=0.412$ ,  $p=0.995$  and  $p=0.512$ , respectively) in cardiovascular disease patients compared with controls. There were no significant differences in serum T3, Progesterone, Estradiol and TSH ( $p=0.443$ ,  $p=0.291$ ,  $p=0.612$  and  $p=0.550$ , respectively) in male cardiovascular disease patients compared to female cardiovascular disease patients. There was a significantly higher level of T4 ( $p=0.042$ ) in male cardiovascular disease patients compared to female cardiovascular disease patients. A significant negative correlation of serum TSH with T4 ( $r=-0.759$ ,  $p=0.000$ ) in cardiovascular disease patients. There was no significant correlation of serum TSH with T3 ( $r=-0.131$ ,  $p=0.560$ ) in cardiovascular disease patients. There was a significant positive correlation of Serum Progesterone with Estradiol ( $r=0.815$ ,  $p=0.000$ ) in cardiovascular disease patients.

**Conclusion:** T4, T3, and TSH serum levels may not be associated with the development of cardiovascular diseases in this environment. Also, serum progesterone may have a linear association with estradiol in cardiovascular disease patients.

*Keywords: Heart disease; sex hormones; thyroid hormones; pituitary gland; menopause.*

## 1. INTRODUCTION

Cardiovascular disease (CVD) is a class of diseases involving the heart or blood vessels. Cardiovascular disease includes coronary artery diseases (CAD) such as angina and myocardial infarction (commonly known as a heart attack), stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart arrhythmia, congenital heart disease, and others [1]. The thyroid hormones (thyroxine and triiodothyronine) are tyrosine-based hormones that are produced by the thyroid gland, which are primarily responsible for the regulation of metabolism, with thyroxine ( $T_4$ ) being the primary form found in the blood and has a higher shelf life [2]. Thyrotrophin (Thyroid Stimulating Hormone) is a glycoprotein hormone synthesised and released by the pituitary gland that regulates the endocrine function of the thyroid gland [3].

Gender has an essential influence on cardiovascular disease, with premenopausal women having lower arterial blood pressure than age-matched men. Compared with premenopausal women, postmenopausal women have higher blood pressures, suggesting that ovarian hormones such as estrogen (estradiol, which is the biologically active form in the blood) and progesterone may modulate the risk of heart disease [4]. Research has shown that female sex hormones play an essential role in cardiovascular pathophysiology and that there are significant sex differences in cardiovascular risk [5]. Some research has it that the level of progesterone and estrogen plays a vital role in

the reduction of cardiovascular diseases in women. However, the authenticity of the information still needs to be questioned. Also, little is known about the association between thyroid function/dysfunction and the risk of cardiovascular diseases. Despite the various research on cardiovascular diseases, the knowledge of the involvement of thyroid and female sex hormones (progesterone and estrogen) remains limited. Hence, this research was done to ascertain if thyroid hormones and female sex hormones (progesterone and estrogen) play a role or are a risk factor in the development of cardiovascular diseases.

## 2. MATERIALS AND METHODS

### 2.1 Study Design

The period of subjects' enrolment, classification administration of questionnaires, sample collection, determination of  $T_4$ ,  $T_3$ , TSH, estrogen, and progesterone, and data generation in this study lasted from November 2017 to July 2018. The study area is Enugu state. The study area serves as the major medical clinic for the poor and rich in Enugu state and its environs.

### 2.2 Study Population

By random sampling, 20 cardiovascular disease subjects (10 males and 10 females) between 40 and 60 years were selected. They were age-matched with 20 non-cardiovascular disease subjects (10 males and 10 females) who were the control subjects.

## 2.3 The Selection Criteria for Patients

### 2.3.1 Inclusion criteria for patients

Patients who manifested a family history of heart failure, Dyspnea (Shortness of breath), and vascular congestion were revealed by chest radiography. Angina pectoris, Rapid/irregular Pulse rate. Electrolyte, Urea, and Creatinine laboratory reports establish mild to moderate renal insufficiency and oedema in the legs (ankles and feet). Electrocardiogram changes, abnormal echocardiogram report, Fatigue and weakness, exercise intolerance, Persistent cough or wheezing with white or blood-stained mucus/catarrh.

### 2.3.2 Exclusion

Exclusion criteria are as follows: Patients who manifested some chronic disease such as HIV/AIDS, liver diseases (hepatitis), Diabetes mellitus/insipidus, and tuberculosis. Subjects without any clinical manifestation of heart disease are healthy individuals. Patients outside the age range for this study. Subjects who refused to give informed consent for this study.

## 2.4 Sample Collection

Five millilitres of venous blood collected from each participant was dispensed into a plain container and centrifuged at 3000 rpm for 10 minutes. The serum was extracted into plain containers and stored refrigerated at -20 till analysis. All samples were analysed within four days of sample collection.

## 2.5 Estimation of the levels of serum T<sub>3</sub>, T<sub>4</sub>, and TSH

A microplate reader model MR-96A (Operon Bio Tech and Health care, Koramangala, Bengaluru, India) was employed for serum T<sub>3</sub>, T<sub>4</sub>, and TSH determination as previously described by Gharib and Chopra for T<sub>3</sub> [6,7], Barker and Chopra for T<sub>4</sub> [7,8], Hopton and Caldwell for TSH [9,10]. Serum progesterone and estradiol were also determined using the same microplate reader described by Radwanska and Muotila [11,12], respectively. The digested samples were analysed using the ELISA methodology, and readings were taken. Repeated analyses of standard solutions confirmed the method's precision.

## 2.6 Statistical Analysis

SPSS version 21 was employed in the statistical analysis of the data obtained. The test of significance was determined by student t-test and Pearson Correlation. Values with P < 0.05 were considered statistically significant. All values were expressed as mean ± standard deviation.

## 3. RESULTS

Table 1 there were no significant differences in serum T<sub>3</sub>, T<sub>4</sub>, and TSH, Progesterone, and Estradiol (p=0.236, p=0.834, p=0.412, p=0.995 and p=0.512 respectively) in cardiovascular disease patients compared with controls.

**Table 1. Serum T<sub>3</sub>, T<sub>4</sub>, TSH, progesterone and estradiol in cardiovascular disease patients versus controls**

VARIABLE (Mean ± SD)	Cardiovascular Disease (n=20)	Controls (n=20)	t-value	p-value
<b>T<sub>3</sub> (ng/ml)</b>	1.80±0.33	1.58±0.59	1.224	0.236
Lower 95% C.I.	1.64	1.30		
Upper 95% C.I.	1.95	1.85		
<b>T<sub>4</sub> (µg/dl)</b>	11.02±2.72	10.83±3.0	0.212	0.834
Lower 95% C.I.	9.74	9.41		
Upper 95% C.I.	12.29	12.24		
<b>TSH(µIU/mL)</b>	1.74±0.61	1.92±0.92	-0.838	0.412
Lower 95% C.I.	1.45	1.48		
Upper 95% C.I.	2.02	2.35		
<b>Progesterone(pg/ml)</b>	1.50±3.44	1.49±2.55	0.007	0.995
Lower 95% C.I.	-0.11	0.29		
Upper 95% C.I.	3.11	2.69		
<b>Estradiol(pg/ml)</b>	75.94±28.68	70.23±35.58	0.669	0.512
Lower 95% C.I.	62.51	53.57		
Upper 95% C.I.	89.36	86.89		

**Table 2. Serum T<sub>3</sub>, T<sub>4</sub>, TSH, progesterone and estradiol in male cardiovascular diseases patients versus female cardiovascular diseases patients**

VARIABLES (Mean ± SD)	Male Cardiovascular Disease Patients (n= 10)	Female Cardiovascular Disease Patients (n=10)	t-value	p-value
<b>T<sub>3</sub> (ng/ml)</b>	1.75±0.45	1.86 ±0.14	-0.803	0.443
Lower 95% C.I.	1.41	1.75		
Upper 95% C.I.	2.06	1.96		
<b>T<sub>4</sub> (µg/dl)</b>	9.40±2.40	12.84±2.01	-2.372	0.042
Lower 95% C.I.	7.69	11.20		
Upper 95% C.I.	11.11	14.07		
<b>TSH (µIU/mL)</b>	1.90±0.54	1.54±0.66	1.121	0.291
Lower 95% C.I.	1.50	1.10		
Upper 95% C.I.	2.29	2.05		
<b>Progesterone(pg/ml)</b>	1.94±4.93	1.18±0.56	0.525	0.612
Lower 95% C.I.	-1.57	0.77		
Upper 95% C.I.	5.47	1.59		
<b>Estradiol (pg/ml)</b>	77.27±39.39	70.64±13.37	0.621	0.550
Lower 95% C.I.	49.09	61.07		
Upper 95% C.I.	105.45	80.21		

**Table 3. Correlation of Serum TSH with T<sub>3</sub> and T<sub>4</sub> in cardiovascular disease patients**

Dependent variables	N	r- value	p-value
T <sub>3</sub>	20	-0.131	0.560
T <sub>4</sub>	20	-0.759**	0.000
Progesterone	20	-0.488*	0.029
Estradiol	20	-0.464*	0.039

**Table 4. Pearson correlation of serum progesterone with estradiol in cardiovascular disease patients**

Dependent variables	N	r-value	p-value
Estradiol	20	0.994**	0.000
T <sub>3</sub>	20	0.108	0.649
T <sub>4</sub>	20	0.403	0.078

Table 2 there were no significant differences in serum T<sub>3</sub>, Progesterone, Estradiol and TSH (p=0.443, p=0.291, p=0.612 and p=0.550, respectively) in male cardiovascular disease patients compared to female cardiovascular disease patients. There was a significant higher level of T<sub>4</sub> (p=0.042) in male cardiovascular disease patients compared to female cardiovascular disease patients.

Table 3 a significant negative correlation of serum TSH with T<sub>4</sub> (r=-0.759, p=0.000) in cardiovascular disease patients. There was no significant correlation of serum TSH with T<sub>3</sub> (r=-0.131, p=0.560) in cardiovascular disease patients.

Table 4 in cardiovascular disease patients, there was a significant positive correlation of Serum Progesterone with Estradiol (r=0.815, p=0.000).

#### 4. DISCUSSION

Cardiovascular diseases are abnormal issues affecting the heart and blood vessels [13]. The development of this disease condition is multifactorial, with a higher risk of cardiovascular disease than pre-menopausal women [14]. This study reveals no significant differences in serum T<sub>3</sub>, T<sub>4</sub>, TSH, progesterone and estradiol in cardiovascular disease patients compared to controls. This could be because of the absence of thyroid dysfunction in the patients. It was found that thyroid function in the clinically normal range was not associated with cardiovascular disease.

In contrast, it was reported that a higher serum concentration of T<sub>3</sub> and T<sub>4</sub> and lower TSH were found in patients suffering from cardiovascular disease (called subclinical hyperthyroidism) [15]. In a 10-year cohort study of older patients, a low

TSH was associated with an increased risk for cardiovascular mortality [16] and atrial fibrillation [17]. Thyroid dysfunction is one of the risk factors for cardiovascular disease [18].  $T_3$  increases the heart rate and force of contraction, thus increasing cardiac output by increasing  $\beta$ -adrenergic receptor levels in the myocardium [19]. This results in increased systolic blood pressure and decreased diastolic blood pressure. A low TSH level is associated with an increased risk for atrial fibrillation, which in turn could lead to congestive heart failure [20]. Hyperthyroidism is characterised by widened pulse pressure. Recent reports have shown that arterial stiffness is increased in hyperthyroidism despite the low systemic vascular resistance (SVR) [21]. Thus, excess thyroid hormone typically causes systolic blood pressure to rise, which can be quite dramatic in older patients with impaired arterial compliance due to atherosclerotic disease. Hyperthyroidism, the most common form of hypertension, has been documented as a secondary cause of isolated systolic hypertension [22]. In hypothyroidism, endothelial dysfunction and impaired vascular smooth muscle cells (VSM) relaxation led to increased SVR [23]. These effects lead to diastolic hypertension in 30% of patients [24]. Also, no significant difference in serum progesterone and estradiol of cardiovascular disease patients compared to control is similar to the research carried out by Wehr et al. [25]; they found no significant change in estradiol and progesterone levels due to the cardiac arrest and resuscitation process in a canine model of ventricular fibrillation arrest. Epidemiological studies have linked lower androgen levels with a higher risk of cardiac disease; however, whether there is a causal role remains unclear [26].

This study showed no significant differences in serum  $T_3$ , TSH, progesterone, and estradiol in male heart disease patients compared to female heart disease patients. There was a significantly higher level of  $T_4$  in male heart disease patients compared to female heart disease patients.  $T_4$  is converted to the active  $T_3$  within cells by deiodinases (5'-iodine). The changes in deiodinase 1 and 2 catalytic properties are higher in subjects with higher fat mass, leading to a higher conversion of  $T_4$  to  $T_3$  [27]. Since females have higher adipose tissue than males, an increased level of deiodinases 1 in adipose tissue stimulates it, leading to leptin production. In turn, it enhances the production of  $T_3$  from  $T_4$  [27]. This could explain the higher level of  $T_4$  in males than females. No significant difference in

serum progesterone and estradiol suggests that the level of progesterone and estradiol is not a predictive factor in diagnosing any form of heart disease. It is in agreement with a recent analysis of cardiovascular diseases in a large cohort of postmenopausal women with regards to the female sex hormones, which showed no clear relationship between the level of estradiol and progesterone and the incidence of cardiovascular diseases [28]. Female sex hormones were considered to play an essential role in reducing the incidence of cardiac disease in premenopausal women. However, the large cohort trials showed no benefit of combined estrogen/progesterone supplementation and possible harm with a greater risk of cardiovascular disease [29]. This raises the question of whether either of these hormones has potentially harmful effects.

This present study showed a significant negative correlation of serum TSH with  $T_4$  in cardiovascular disease patients. This means serum TSH increases as  $T_4$  decreases in cardiovascular disease patients [15,30]. This was also mentioned by Johansen et al. in their research, in which there was a significant negative correlation of serum TSH with  $T_4$  [31]. The negative feedback mechanism could explain this. Production of  $T_3$  and its prohormone thyroxine ( $T_4$ ) is activated by thyroid-stimulating hormone (TSH), which is released from the anterior pituitary gland. This pathway is part of a closed-loop feedback process. Elevated concentrations of  $T_3$  and  $T_4$  in the blood plasma inhibit the production of TSH in the anterior pituitary gland. As concentrations of these hormones decrease, the anterior pituitary gland increases production of TSH. By these processes, a feedback control system stabilises the amount of thyroid hormones in the bloodstream [32]. Serum TSH with  $T_3$  in cardiovascular disease patients had no significant correlation.

In contrast, Johansen et al. reported a significant correlation of serum TSH with  $T_3$ . Still, they later stated that the correlation coefficients dropped to non-significant levels when partial correlation analysis considered and eliminated interdependence between the  $T_3$  and  $T_4$  indices [31]. There was a significant positive correlation between serum progesterone and estradiol, indicating a linear relationship between progesterone and estradiol levels in cardiovascular diseases.

## 5. CONCLUSION

Thyroid dysfunction affects the heart either by producing too little thyroid hormone (a condition called hypothyroidism) or too much thyroid hormone (called hyperthyroidism). Thyroid dysfunction is a risk factor for cardiovascular disease. Thyroid function in the clinically normal range is not associated with cardiovascular disease. Hence, this study concludes that serum T4, T3, and TSH levels may not be related to the development of cardiovascular diseases in this environment. This study also concludes that serum progesterone may have a linear association with estradiol in cardiovascular disease patients.

## CONSENT AND ETHICAL APPROVAL

The Ethical Advisory Committee of Enugu State University Teaching Hospital (ESUTH) approved the research protocol. Informed consent and approval of all the subjects were obtained. Each participant signed a consent form after the procedure, and implementations were explained to the subject in English or the local Igbo dialect. Participation was voluntary, and participants could withdraw from the study at any time.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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