Journal of Advanced Zoology

ISSN: 0253-7214
*Volume **44** Issue **03 Year 2023** Page **1235:1241***

The Impact of Hypothyroidism on Clinical Outcomes in Patients Undergoing Percutaneous Coronary Intervention

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Article History

Received: 06 June 2023
Revised: 05 Sept 2023
Accepted: 09 Nov 2023

Abstract

Introduction: Hypothyroidism either subclinical (SCH) or overt is independently associated with an increased risk of coronary artery disease (CAD). The combined effects of SCH and overt hypothyroidism on clinical outcomes after percutaneous coronary intervention (PCI) are largely unknown. Aim: The aim of the study is to assess the impact of subclinical and overt hypothyroidism among patients presenting with CAD undergoing PCI. Materials and Methods: A total of 102 patients who were referred to the Madras Medical Mission Hospital for PCI from September 2020 to March 2021 were enrolled in the study. These patients were categorized into three groups. Each group has 34 patients and was followed for one year. Group 1: Patients with normal TSH levels (TSH-0.45 -5mlU/Liter) and euthyroid at T_3, T_4 levels. Group 2: Patients with subclinical hypothyroidism with elevated TSH levels (TSH=5-15mlU/liter) and normal thyroid with T_3, T_4 levels. Group 3: Patients with a family history of overt hypothyroidism or high TSH levels(<15mlU/liter) and low T_3 and T_4 levels [16]. Results: We applied ANOVA to find the PCI outcomes. A p-value of <0.05 was accepted as significant. Age (p-0.03), recent myocardial infarction (p-0.04), diabetes mellitus (p<0.001), HbA1C (p-0.012), and systolic blood pressure (p-0.04) were found to be significant. Post-PCI bleeding complications (p<0.001) during one month, six months, and one-year follow-up were the main observation of the study. Conclusion: The prior history of DM and elevated HbA1c levels observed in the overt hypothyroid group indicate that DM was one of the key factors associated with overt hypothyroidism. Despite the fact that PCI was safe for patients with hypothyroidism, the risk of early post-PCI bleeding was of concern.

Keywords: *Hypothyroidism, Coronary artery disease, Percutaneous coronary intervention, Major adverse cardiovascular events, Diabetes mellitus.*

1. Introduction

Background:

The cardiovascular system is one of the principal targets of thyroid hormones. Hypothyroidism either subclinical or overt have been independently associated with an increased risk of coronary artery disease (CAD) which is associated with adverse cardiovascular events. The combined effects of subclinical hypothyroidism (SCH) and overt hypothyroidism on clinical outcomes after percutaneous coronary intervention (PCI) are largely unknown.

Thyroid function has a profound effect on the cardiovascular system [1]. Thyroid hormones indirectly affect muscle cells by activating the inflammatory immune responses through genomic and non-genomic mechanisms [2]. A lack of adequate thyroid hormones results in adverse effects such as

endothelial dysfunction and increased inflammation [3]. Hypothyroidism is diagnosed when thyroid hormone levels are low and thyroid stimulating hormone (TSH) levels are elevated, whereas SCH is defined as elevated TSH levels above the upper assay reference range for normal thyroid hormone levels [4]. Epidemiological studies have shown increased cardiovascular risk in patients with both subclinical and overt hypothyroidism [5].

The concept of mild or SCH has emerged over the last few decades. SCH is estimated to occur in 4% to 20% of the adult population [6]. Previous studies have confirmed the existence of an association between SCH or overt hypothyroidism and CAD, especially in patients younger than 65 years of age. TSH levels in the upper part of the reference range are associated with worse cardiovascular risk profiles [7]. Although subclinical thyroid dysfunction may increase cardiovascular risk, it has been established that it may have a greater impact on cardiovascular risk in contrast to dyslipidemia, diabetes mellitus, and hypertension [8]. TSH receptors are expressed on vascular endothelial cells, and elevated TSH has been shown to promote endothelial dysfunction by altering gene expression in human umbilical vein endothelial cells (HUVECs) [9]. SCH is rarely diagnosed in STEMI (ST segment elevation myocardial infarction) patients treated with primary PCI. It is an important predictor of poor in-hospital outcomes and increased short and long-term mortality [10].

Coronary endothelial dysfunction paves the way to atherosclerosis. This is associated with the exacerbation of cardiovascular events in patients with hypothyroidism [11]. Individuals with overt hypothyroidism have been reported to be at risk for cardiovascular abnormalities and CAD, and accelerated atherosclerosis [12]. Clinical studies confirm that lower T_3(thyroxine) is associated with greater thrombotic burden [13], in patients with acute coronary syndrome (ACS) [14]. Hypothyroidism is also associated with adverse outcomes in patients undergoing PCI. Post-PCI patients with overt or SCH have more major adverse cardio and cerebrovascular events (MACCE) and greater progression of angiographic CAD compared to euthyroid patients [15].

This suggests that lack of adequate thyroid hormones has other adverse effects on clinical outcomes undergoing revascularization. This study focuses on the clinical outcome in patients with SCH and overt hypothyroidism undergoing PCI.

Aim:

To study the impact of subclinical hypothyroidism and overt hypothyroidism among patients presenting with CAD undergoing PCI.

2. Materials And Methods

A total of 102 patients who were referred to the Madras Medical Mission Hospital for PCI from September 2020 to March 2021 were enrolled in the present study. The approval for collection of patients sample and data was approved by Institutional Ethics Committee. These patients were categorized into three groups. Each group has 34 patients and were followed for one year.

Group 1: Patients with normal TSH (TSH=0.45 -5mlU/Liter) and euthyroid at T_3, T_4 levels.

Group 2: Patients with subclinical hypothyroidism with elevated TSH levels (TSH=5-15mlU/liter) and normal thyroid with T_3 and T_4 levels.

Group 3: Patients with a family history of overt hypothyroidism or high TSH levels(<15mlU/liter) and low T_3 and T_4 levels [16].

Venous blood samples were taken from patients for evaluation of biochemical parameters.

Adult free T_3 was in the normal range of 3.2-6.8 pmol/L.

Adult free T_4 was in the normal range of 10.3-34.7 pmol/L.

All the above assays were performed on the VITROS 7600 using an enhanced electrochemiluminescence assay.

Inclusion criteria

- CAD patients undergoing PCI
- Age ≥ 18 years.
- Able to provide informed consent and not meet exclusion criteria.

Exclusion criteria

- Hyperthyroidism
- Other endocrine disorders such as pheochromocytoma.

- Unable to understand or sign consent forms.

Patients who met inclusion and exclusion criteria were selected for the study. Selected patients were followed for one year. Continuous variables were presented as means and standard deviations. Categorical variables were presented as frequencies (percentages). ANOVA (analysis of variance) was used to examine whether the parameters significantly affect CAD severity and outcome. A p-value <0.05 was accepted as significant.

3. Results and Discussion

Parameters such as age (61.1 ± 8.4, 61.7 ± 7.2, 56.6 ± 9.9, p-0.03), MI<90 days (24 (70.6%), 14 (41.2%), 21 (61.8%), p-0.04), diabetes mellitus (17 (50%), 23 (67.6%), 34 (100%), p<0.001), glycated hemoglobin (7.8 ± 1.8, 8.1 ± 2.5, 9.3 ± 1.9, p-0.012) and systolic blood pressure (129 ± 18.7, 142.2 ± 21.4, 134.9 ± 23.5, p-0.04) were found to be significant. Various other parameters including demographics and medical history, laboratory tests, procedural details, blood tests after outpatient care, and in-hospital events, showed no association between these specific patient groups. Among major adverse cardiovascular events (MACE), bleeding events were found to be significant during the follow-up of one month (2 (5.9%), 1 (3.2%),0, p<0.001), six months (2 (6.5%), 1 (3.8%),0, p<0.001), and one year (2 (7.1%), 1 (3.8%),0, p<0.001).

Table 1: Patient history and Demographics

Parameters	GROUP I (n=34)	GROUP II (n=34)	GROUP III (n=34)	P value
Age(years)	61.1 ± 8.4	61.7 ± 7.2	56.6 ± 9.9	0.03*
Males (%)	26 (76.5%)	26 (76.5%)	27(79.4%)	0.9
Female (%)	8 (23.5%)	8 (23.5%)	8 (20.6%)	
Height(cm)	163.7 ± 7.3	162.7 ± 8.7	160.4 ± 5.4	0.3
Weight(kg)	70.6 ± 9.8	66.6 ± 11.8	67.9 ±10.2	0.3
BMI	26.3 ± 3.1	25.1 ± 3.5	26.9 ±6.1	0.3
DM	17 (50%)	23 (67.6%)	34 (100%)	<0.001*
HTN	15 (44.1%)	16 (47.1%)	17 (50%)	0.6
Dyslipidemia	6 (17.6%)	2 (5.9%)	5 (14.7%)	0.3
Smoking	1 (2.9%)		2 (5.9%)	0.4
Prior CVA	1 (2.9%)	2 (5.9%)	1 (2.9%)	0.7
Prior CKD	1 (2.9%)	1 (2.9%)	1 (2.9%)	1
Prior PVD	0	1 (2.9%)	0	0.3
Prior CAD	5 (14.7%)	10 (29.4%)	8 (23.5%)	0.3
Prior PCI	3 (8.8%)	3 (8.8%)	-	0.2
Prior CABG	1 (2.9%)	1 (2.9%)	1 (2.9%)	1
UA	5 (14.7%)	5 (14.7%)	5 (14.7%)	0.9
NSTEMI	4 (11.8%)	9 (26.5%)	3 (8.8%)	0.1
MI < 90 days	24 (70.6%)	14 (41.2%)	21 (61.8%)	0.04*
Thrombolysed	14 (41.2%)	8 (23.5%)	10 (29.4%)	0.3
CS	-	-	1 (2.9%)	0.3
LVEF	41.2 ± 11.3	45.5 ± 8.3	41 ± 12	0.2

Foot Note: BMI- Body Mass Index, HTN – Hypertension, CVA – Cerebrovascular Accident, CKD – Chronic Kidney Disease, PVD – Peripheral Vascular Disease, CAD-Coronary Artery Disease, PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Graft, UA – Unstable Angina, NSTEMI – Non ST-elevation MI, MI- Myocardial Infarction, CS – Cardiogenic shock, LVEF-Left Ventricular Ejection Fraction.

Table 2: Laboratory Investigations

Parameters	Group I (n=34)	Group II (n=34)	Group III (n=34)	P value
Hb(g/dl)	13.3 ± 1.9	12.7 ± 1.9	13.1 ± 2.2	0.4
Platelets(lak/Cmm)	2.6 ± 0.6	2.8 ± 1	2.7 ± 0.9	0.4
Urea(mg/dl)	28.1 ± 11.3	30 ± 19.7	28.7 ± 24.1	0.9

Creatinine(mg/dl)	0.8 ± 0.4	0.9 ± 0.3	0.9 ± 0.5	0.9
CK NAC (IU/L)	401.78 ± 530.6	664.9 ± 520	1066.2 ± 708	0.4
CKMB (ng/dl)	26.2 ± 49	47 ± 32.5	50.9 ± 36	0.3
Troponin I(ng/dl)	12.7 ± 17.1	4.3 ± 8.9	9.8 ± 17.4	0.2
Triglycerides(mg/dl)	184.1 ± 114	149.6 ± 47	226 ± 172.9	0.2
Total cholesterol(mg/dl)	164.6 ± 43.9	154.4 ± 37.5	181 ± 62.2	0.3
HDL (mg/dl)	40 ± 19.8	35.2 ± 11.7	35.6 ± 12.8	0.5
LDL (mg/dl)	109.6 ± 44.1	102.7± 36.7	113.3 ± 57.9	0.8
HbA1C (%)	7.8 ± 1.8	8.1 ± 2.5	9.3 ± 1.9	0.012*

Foot note: Hb – Hemoglobin, CK NAC – Creatinine Kinase NAC, CKMB – Creatinine Kinase MB, HDL- High Density Lipoprotein, LDL – Low Density Lipoprotein, HbA1C – Glycosylated Haemoglobin.

Table 3: Procedural details

Parameters	Group I (n=34)	Group II (n=34)	Group III (n=34)	P value
HR (bpm)	81.2 ± 12.5	81.5 ± 16.1	80.5 ± 11	0.9
Systolic BP (mmHg)	129 ± 18.7	142.2 ± 21.4	134.9 ± 23.5	0.04*
Diastolic BP (mmHg)	76.7 ± 8.8	75.4 ± 10.5	76.4 ± 13.3	0.8
Mean BP (mmHg)	98.5 ± 11.8	104.3 ± 15.6	97.9 ± 15	0.1
SVD	14 (41.2%)	13 (38.2%)	15 (44.1%)	0.9
DVD	15 (44.1%)	15 (44.1%)	15 (44.1%)	
TVD	5 (14.7%)	5 (14.7%)	4 (11.8%)	
LEFT MAIN	-	1 (2.9%)	-	
LAD	20 (58.8%)	22 (64.7%)	27(79.4%)	0.2
LCX	5 (14.7%)	8(23.5%)	5 (14.7%)	0.5
RCA	16 (47.1%)	12 (35.3%)	10(29.4%)	0.3
ISR	1 (2.9%)	1 (2.9%)	-	0.6
SVG	-	1 (2.9%)	-	0.4
IABP	2 (5.9%)	1(2.9%)	3 (8.8%)	0.6
TPI	-	-	1(2.9%)	0.3

Foot note: HR – Heart Rate, Sys BP – Systolic Blood Pressure, Dia BP – Diastolic Blood Pressure, SVD – Single Vessel Disease, DVD – Double Vessel Disease, TVD – Triple Vessel Disease, LAD – Left Anterior Descending Artery, LC_X – Left Circumflex Artery, RCA – Right Coronary Artery, LM – Left Main canal, ISR –Instent Restenosis, SVG – Saphenous Vein Graft, IABP – Intra-Aortic Baloon Pump, TPI – Temporary Pacemaker Implantation.

Table 4: Post OP Blood Investigations

Parameters	Group I (n=34)	Group II (n=34)	Group III (n=34)	P value
Post Hb(gm/dl)	12.6 ± 1.8	12.5 ± 1.7	12.2 ± 1.9	0.6
Post Ur(mg/dl)	26.9 ± 9.9	26.6 ± 14.6	31.4 ± 30.7	0.6
Post Cr(mg/dl)	0.8 ± 0.4	0.8 ± 0.3	0.8 ± 0.4	0.9

Foot note: Post Hb – Post hemoglobin, Post Ur – Post Urea, Post Cr – Post Creatinine

Table 5: In Hospital Events

Parameters	Group I (n=34)	Group II (n=34)	Group III (n=34)	P value
Duration of hospital stay	4.1 ± 2	4.1 ±2.1	4.6 ± 3.1	0.5
Bleeding	2 (5.9%)	1 (2.9%)	-	0.4
Death	-	-	1 (2.9%)	0.3

Table 6: One month follow-up

Parameters	GROUP I (n=34)	GROUP II (n=31)	GROUP III (n=30)	P value
Bleeding	2 (5.9%)	1 (3.2%)	-	<0.001*
CVA		-	-	

MI	-	-	-	
Repeat revascularization	-	-	-	
Death	-	-	1 (3.3%)	0.3

Foot note: CVA-Cerebrovascular accident, MI-Myocardial infarction

Table 7: Six-month follow-up

Parameters	GROUP I (n=31)	GROUP II (n=26)	GROUP III (n=21)	P value
Bleeding	2 (6.5%)	1 (3.8%)	-	<0.001*
CVA	-	-	-	-
MI	1(32.2%)	-	-	-
Repeat revascularization	-	-	-	-
Death	-	-	1 (4.7%)	0.3

Foot note: CVA-Cerebrovascular accident, MI-Myocardial infarction

Table 8: One year follow-up

Parameters	GROUP I (n=28)	GROUP II (n=26)	GROUP III (n=20)	P value
Bleeding	2 (7.1%)	1 (3.8%)	-	<0.001*
CVA	-	-	-	-
MI	1 (3.6%)	-	-	-
Repeat revascularization	-	-	-	-
Death	-	-	1 (5%)	0.3

Foot note: CVA-Cerebrovascular accident, MI-Myocardial infarction

The present study was conducted to assess the impact of SCH and overt hypothyroidism on cardiovascular outcomes in patients undergoing PCI. Among the three groups compared, overt hypothyroidism (Group III) was significant in terms of age, diabetes mellitus, and HbA1c. Bleeding events were significant, but one patient with SCH and two with euthyroidism were not sufficient to draw firm conclusions.

The first observation was that overt hypothyroidism was confirmed significantly younger than the other two groups (61.1 ± 8.4, 61.7 ± 7.2, 56.6 ± 9.9, p-0.03). Previous studies have confirmed the existence of an association between SCH or overt hypothyroidism and CAD, especially in patients <65 years of age. [7]

A second key observation of the present study was that all patients with overt hypothyroidism had diabetes mellitus (DM) and 67% of the patients with SCH had DM (17 (50%), 23 (67.6%), 34 (100%), p<0.001). The previous studies found that 1.93-fold increased risk associated with the incidence of SCH in patients with type 2 diabetes mellitus(T2DM) resulting in microvascular complications. DM affects thyroid function by controlling TSH release at the hypothalamic level and affecting T_4 to T_3 conversion in peripheral tissues. Glucose utilization was slowed in the peripheral tissues, and glucose oxidation and glycogen synthesis were slowed in hypothyroidism. The inability of insulin to adequately maintain glucose utilization by muscles leads to insulin resistance in patients with subclinical and overt hypothyroidism [17]. Several studies have documented an increased prevalence of thyroid disorders in DM patients and vice versa. Subclinical and overt hypothyroidism was the most common form of thyroid dysfunction in T2DM.

Analyzing the laboratory tests, HbA1c values were found significant (7.8 ± 1.8, 8.1 ± 2.5, 9.3 ± 1.9, p-0.012) in the presence of overt hypothyroidism. According to the study done by Bhattacharjee.R et al (2018) stated that HbA1c levels were found to be critically significant in overt hypothyroidism, which was manifested due to low red blood cell turnover [18]. In another study, changes in serum TSH correlated with changes in which was associated with an increased risk of T2DM [6].

Furthermore, systolic blood pressure was higher in the SCH group were compared to the other two groups (129 ± 18.7, 142.2 ± 21.4, 134.9 ± 23.5, p-0.04). This was supported by several studies that found that systolic blood pressure in SCH patients was higher than in euthyroid subjects [19]. Even with elevated serum TSH levels, the prevalence of hypertension was increased significantly from the euthyroid to SCH and was stronger in patients less than 65 years [20]. The underlying cause was related to the level of systemic vascular resistance present in patients with subclinical hypothyroidism. T_3 could act directly on arterial smooth muscle cells in blood vessels to cause vasodilation [21]. Decreased T_3 levels lead to increased vascular resistance, leading to increased blood pressure. Luboshitzky et al

(2002) found that the prevalence of hypertension in the SCH group was significantly higher than that in the normal control group, supporting our conclusions [22].

It was also observed that an increased frequency of bleeding among patients were monitored during the follow-up of one month (2 (5.9%), 1 (3.2%),0, p<0.001), six months (2 (6.5%), 1 (3.8%),0, p<0.001), and one year (2 (7.1%), 1 (3.8%),0, p<0.001). Perioperative bleeding was one of the most common complications of PCI. Neither bleeding event occurs in patients with overt hypothyroid but does occur in patients with SCH. Previous studies had shown that hypothyroidism can lead to a hypocoagulable state due to reduced synthesis of clotting factors such as von Willebrand factor antigen and factor VIII. Interaction between thyroid hormone and beta-adrenergic receptors induces the release of VWF from endothelial cells. Thyroid hormone deficiency downregulates VWF synthesis in endothelial cells and releases it into circulation. Consequently, hypothyroidism makes the endothelium less sensitive to adrenergic stimulation [23]. TSH in the upper part of the reference range was associated with in-hospital bleeding. Strong evidence of an association between bleeding and hypothyroidism has been reported in ACS patients [7]. In contrast in the present study, the risk of bleeding appears to be higher in the euthyroid patients compared with SCH.

4. Conclusion

In the current study, SCH patients were observed to have 67.6% DM when compared with 100% DM in patients with overt hypothyroidism, suggesting that overt hypothyroidism and DM were closely related. In addition, HbA1C levels in patients with overt hypothyroidism (9.3 ± 1.9) were higher than those in SCH patients (8.1 ± 2.5), indicating that HbA1C levels were significantly associated with overt hypothyroidism. The prior history of DM and elevated HbA1c levels observed in the overt hypothyroid group indicate that DM was one of the key factors associated with overt hypothyroidism. HbA1C levels can also be influenced by patient-dependent factors such as dietary management, physical activity, and compliance with drugs. On the other hand, this study recommends routine diagnostics of CAD patients' thyroid profiles prior to PCI. These patients may require special precautions to control both hypothyroidism and T2DM in the early stages after PCI. Despite the fact that PCI was safe for patients with hypothyroidism, the risk of early post-PCI bleeding was of concern. But as per the present study, the statistical significance does not evidence to prove bleeding concerns. A larger meta-analysis was needed to assess the severity of CAD patients undergoing PCI and the association between SCH and hypothyroidism.

No Conflict of Interest:
No funding sources

Acknowledgments:
We declare that all the authors have no conflict of interest. The authors thank all the staff at Catheterization Laboratory, The Madras Medical Mission and the subjects who participated in this study.

References:

1. Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH, *et al*. Effects of thyroid hormones on the heart.*Clin Invest.Arterioscl*.2014; 26:296-309.
2. Jabbar A, Pingitore A, Pearce SH, *et al*. Thyroid hormones and cardiovascular disease.*Nat Reviews cardiol*. 2017;14:39-55.
3. Ushakiran P, Sandeesha V, Lakshmanakumar N, *et al*. Role of hypothyroidism in dyslipidemia and blood glucose regulation. *Perspectives in Medical Research*.2019; 7: 56-61.
4. Udovcic M, Pena RH, Patham B, *et al*. Hypothyroidism and the Heart.*Methodist Debakey Cardiovasc J.* 2017; 13: 55–59.
5. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al. Thyroid Studies Collaboration . Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304(12):1365–1374. [PMC free article] [PubMed] [Google Scholar]
6. Cooper DavidS, Biondi Bernadette. Subclinical thyroid disease, Lancet. 2012;379:1142–1154. [PubMed] [GoogleScholar]
7. Ndrepepa G, Braun S, Mayer K, *et al*. Prognostic value of thyroid-stimulating hormone within reference range in patients with coronary artery disease. Metabolism. 2015 ;64(10):1308-15.
8. Sun J,Yao L, Fang Y, *et al*. Relationship between subclinical thyroid dysfunction and the risk of cardiovascular outcomes : a systematic review and meta analysis of prospective cohort studies. *Int.JEndocrinol*. 2017; 2017:8130796.
9. Tian L, Zhang L, Liu J, *et al*. Effect of TSH on the function of human umblical vein endothelial cells. J Mol Endocrinol.2014;52: 215-222.
10. Izkhakov E, Zahler D, Rozenfeld KL, *et al*. Unknown subclinical hypothyroidism and in-hospital outcomes and short- and long-term all-cause mortality among ST segment elevation myocardial infarction patients undergoing percutaneous coronary intervention. J Clin Med.2020; 9: 3829.

11. Jaskanwal D Sara, Ming Zhang , HosseinGharib, *et al*. Hypothyroidism Is AssociatedWith Coronary Endothelial Dysfunction in Women. *Journal of the American Heart association.2015;4(8).*
12. Grais, I.M, Sowers, J.R. Thyroid and the Heart. *Am. J. Med.* 2014, *127*, 691–698. [GoogleScholar] [CrossRef] [PubMed]
13. Vishwanathan G, Balasubramaniam K, Hardy R, *et al*. Blood thrombogenicity is independently associated with serum TSH levels in post -non -ST elevation acute coronary syndrome. *J Clin Endocrinol Metab*.2014: 99(6): 2013 -3062.
14. Cao Q, Jiao Y, Yu T, *et al* . Association between mild thyroid dysfunction and clinical outcome in acute coronary syndrome undergoing percutaneous coronary intervention.*Cardiol J*. 2020;27:262-271.
15. Zhang M, Sara JD, Matsuzawa Y,*et al*. Clinical outcomes of patients with hypothyroidism undergoing percutaneous coronary intervention . *Eur Heart J*. 2016;37:2055-65.
16. Larsen R, Kronenberg M, Melmed.S, Polonsky.S. William Textbook of endocrinology, 10th edition. ISBN 0-7216-9184-6. Philadelphia,W.B.Saunders Company,2003,1927 pp
17. Biondi B, Kahaly GJ, Robertson RP. Thyroid Dysfunction and Diabetes Mellitus: Two Closely Associated Disorders. Endocr Rev. 2019 Jun 1;40(3):789-824.
18. R Bhattacharjee et al. Effects of thyroid status on glycatedhemoglobin. Indian J Endocrinol Metab. 2017 Jan-Feb;21(1):26-30.
19. Cai, Y., Ren, Y. & Shi, J. Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. *Hypertens Res* 34, 1098–1105 (2011).
20. Wang X, Wang H, Yan L, Yang L, et al. The Positive Association between Subclinical Hypothyroidism and Newly-Diagnosed Hypertension Is More Explicit in Female Individuals Younger than 65. Endocrinol Metab (Seoul). 2021 Aug;36(4):778-789.
21. Ojamaa K, Klemperer JD, Klein I . Acute effects of thyroid hormone on vascular smooth muscle. *Thyroid* 1996; 6: 505–512.
22. Luboshitzky R, Aviv A, Herer P, LavieL . Risk factors for cardiovascular disease in women with subclinical hypothyroidism. *Thyroid* 2002; 12: 421–425.
23. Vasiliki Kyriazi. The role of von Willebrand factor alterations in thyroid disorders., J Bas Res Med Sci 2020; 7(3):47-61.