e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13(9); 182-187

Original Research Article

Study of Thyroid Dysfunction in Type 2 Diabetes Mellitus: A Comparative Cross-Sectional Study

Sunil H. Tetambe[1], Kamalakar B. Mane[2], Shinde Vitthal[3]

[1]Assistant Professor, Department of Biochemistry, Dr. Balasaheb Vikhe Patil Rural Medical College, Pravara Institute Of Medical Sciences, Loni, Maharashtra.
[2]Associate Professor, Department of Biochemistry, Dr. VMGMC Solapur, Maharashtra, India.
[3]Associate Professor Department of Biochemistry, Dr. Balasaheb Vikhe Patil Rural Medical College, Pravara Institute Of Medical Sciences, Loni. Maharashtra.

Received: 22-06-2023 / Revised 27-07-2023 / Accepted 14-09-2023
Corresponding author: Dr. Shinde Vitthal
Conflict of interest: Nil

Abstract:

Background: Type 2 diabetes mellitus (T2DM) is most predominant and thyroid dysfunction is second most predominant endocrine disorder in India. Thyroid dysfunction may increase the risk of cardiovascular events as well as alters insulin requirements in T2DM patients.

Materials and Methods: Aim of the present study was to find the prevalence of thyroid dysfunction in type 2 diabetes mellitus as compared to non-diabetic subjects. In this study, we included 100 type 2 diabetic subjects and 100 non-diabetic healthy subjects who attended OPD and admitted in medical wards of Dr. VMGMC, Solapur from October 2020 to October 2021. All these subjects were investigated for serum fasting and 2-hour postprandial sugar, total triiodothyronine(T3), total thyroxine (T4) and Thyroid stimulating hormone (TSH).

Results: Difference of values obtained for all three parameters (T3, T4 and TSH) between type 2 diabetics and non-diabetics was compared by using student unpaired t-test using mean and standard deviation (SD) and for all the three parameters p value was <0.001. This means difference observed between type 2 diabetics and non-diabetics for all these three parameters was highly significant. Prevalence of thyroid dysfunction in type 2 diabetics was 56% (54% hypothyroidism, 2% hyperthyroidism) and that in non-diabetics was 30% (29% hypothyroidism, 1% hyperthyroidism).

Conclusion: Prevalence of thyroid dysfunction was significantly higher in type 2 diabetics (56%) than non-diabetic subjects with hypothyroidism being most predominant type of thyroid dysfunction.

Keywords: Diabetes Mellitus; Hypothyroidism; Hyperthyroidism; Thyroxine.

Introduction

World Health Organization (WHO) defines diabetes mellitus as a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in the insulin secretion, insulin action, or both [1]. India has the highest prevalence (estimated 65.1 million) of type 2 diabetes mellitus (T2DM) disease in the world and hence WHO considered India as the diabetic capital of the world [2]. Diabetes mellitus is the most predominant endocrine disorder in clinical practice [3].

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality for patients with type 2 diabetes mellitus (T2DM) [4]. Thyroid dysfunction is second most predominant endocrine disorder in clinical practice [3]. Thyroid dysfunction is a spectrum of disorders of the thyroid gland which manifest either as hyperthyroidism or hypothyroidism and is reflected in the circulating levels of thyroid stimulating hormone (TSH), T4 (Thyroxine), and T3 (Tri-iodothyronine) [5,6,7].

Most predominant form of thyroid dysfunction is hypothyroidism [8,9]. In addition to being direct cardiovascular risk factor, hypothyroidism contributes to cardiovascular morbidity by enhancing other risk factors like hyperlipidemia and hypertension. [8,9].

Subclinical hypothyroidism of moderate severity is associated with higher risk of heart failure and stroke in the younger population [10]. In contrast, in spite of low plasma LDL levels in hyperthyroidism, it is associated with myocardial infarction with normal coronary arteries and recurrent pulmonary embolism. This hypercoagulability in hyperthyroid

patients is likely due to an increase in factor X activity [11].

As both diabetes mellitus and thyroid dysfunction are two most common endocrine disorders, it is common for an individual to be affected by both diabetes mellitus and thyroid dysfunction. In few studies prevalence of thyroid dysfunction among diabetes varies from 31% to 46.5%, most predominant being subclinical hypothyroidism [3]. As insulin and thyroid hormone are intimately involved in cellular metabolism, excess or deficit of either of them result in the functional derangement of the other [12].

Study of interdependent relationship between diabetes and thyroid disease will help guide clinicians on the optimal screening and management of both these conditions [13]. Type 2 diabetes and hypothyroidism are chronic diseases which frequently require lifelong follow up and treatment. Both the diseases have long lasting effects on cardiovascular health and mortality with a higher risk attributable to the type 2 diabetes mellitus [14].

Against all this background, early detection of thyroid dysfunction will help clinicians to decrease morbidity and mortality due to cardiovascular diseases in type 2 diabetes mellitus patients and will also improve quality of life.

Ethical approval: The study is approved by Institutional Ethics Committee, Approval letter no. 22/19 dated 4/10/19.

Methodology:

Aim of present study was to find out prevalence of thyroid dysfunction in type 2 diabetes mellitus as compared to non-diabetics.

This was comparative cross-sectional study, conducted in Department of Biochemistry of Medical College. The study was approved by Institutional Ethics Committee for research work. The study population consisted of 100 subjects of T2DM patients as Cases and 100 subjects without T2DM disease as Controls. After explaining all details, informed consent was taken from each subject for participation in this study. History of patient was recorded in case record form. Subjects were included in study as per inclusion criteria and excluded as per exclusion criteria.

Inclusion Criteria:

1. All cases of type 2 diabetes mellitus [T2DM] irrespective of blood pressure status attending to Out Patient Department (OPD clinic) and medical wards in tertiary care center.
2. As controls, non-diabetic volunteers with not having any known endocrine disorder nor any other disease that may affect thyroid function.
3. Those who had no thyroid surgery nor trauma to the neck.
4. Subjects with no history of previous exposure of radiation to neck.
5. Those type 2 DM patients who give informed consent to the study.
6. Age matched cases and controls were enrolled in study.

Exclusion Criteria:

1. All type 2 DM patients with diseases that may affect thyroid dysfunction are excluded.
2. All type 2DM patients on a medication that can affect thyroid function are excluded. For example: lithium, amiodarone, interferon alpha, iodides, beta blockers, carbimazole, propylthiouracil, potassium iodide, lugols iodine.
3. All patients with diseases, diabetic ketoacidosis (DKA) and chronic renal failure (CRF) are excluded.
4. Those with h/o neck trauma or surgery are excluded.
5. Pregnant women are excluded from study.
6. Subjects with h/o previous exposure of radiation in neck.
7. Non consenting type 2 DM patients and controls.
8. Patients previously diagnosed to have type 1 DM.
9. Prediabetic subjects excluded from study.
10. Subjects receiving lipid lowering drugs like statins are excluded from study.

After inclusion of subjects in study, 5 ml of blood samples of all subjects in study were taken. For glucose estimation, blood samples fasting and post-prandial were taken in fluoride bulb. For all other estimations in study, blood samples were taken in plain bulb. Fasting blood samples were taken for thyroid profile. All blood samples were then centrifuged to obtain serum. Serum glucose estimations were performed on ERBA XL 640 Fully Automatic Spectrophotometric Analyzer.

Thyroid profile was performed on Cobas e411 Fully Automatic Electro Chemiluminescence Immunoanalyzer. After obtaining all the results, 'Master Chart' prepared and statistical analysis was done by using statistical analysis programme in Microsoft XL sheet software. Results of two groups were compared by using 'unpaired t test' statistical analysis method to obtain p value.

Reference values that were used to diagnose T2DM and thyroid dysfunction were as following:

Reference ranges:

Reference range for glucose:

- **Normal [15]:**
  - Fasting plasma glucose < 100 mg/dl or

- 2 hour after 75 g glucose < 140 mg/dl.

Diabetes [15]:

- fasting plasma glucose ≥126 mg/dl or
- Random or 2 hours after 75 g glucose ≥200 mg/dl.

Prediabetes [15]:

- Fasting plasma glucose 100 -125 mg/dl or
- 2 hours after 75 g glucose 140 -199 mg/dl.

Reference range for thyroid profile:

- T3: 1.30 – 3.10 nmol/l [16]
- T4: 66-181 nmol/l [17]
- TSH: 0.270- 4.20 uIU/ml [18]

Guidelines for detection of thyroid dysfunction [6,19]:

Normal: When T3, T4 and TSH were in reference range.

Primary Overt hypothyroidism: Irrespective of clinical features when

- TSH more than 4.20 µIU/ml and
- T3 less than 1.30 nmol/l and/or
- T4 less than 66 nmol/l.

Primary Overt hyperthyroidism: Irrespective of clinical features when

- TSH less than 0.270 µIU/ml and
- T3 more than 3.10 nmol/l and/or
- T4 more than 181 nmol/l.

Primary Subclinical hypothyroidism: Irrespective of clinical features when

- TSH more than 4.20 µIU/ml and
- T3 and T4 are within reference range.

Primary Subclinical hyperthyroidism: Irrespective of clinical features when

- TSH less than 0.270 µIU/ml and
- T3 and T4 are within reference range.

Parameters in study were estimated by following methods.

1. Fasting and post prandial blood sugar levels is estimated by Glucose Oxidase- Peroxidase (GOD-POD) method [20].
2. Tri-iodothyronine (T3) [16], Thyroxine (T4) [17], Thyroid stimulating hormone (TSH) [18] is estimated by Electrochemiluminescence immunoassay **(**ECLIA).

Observations & Results:

Table 1: p values for different parameters for comparison between cases and controls.

Parameter	Cases (Mean ± SD)	Controls	p value significance
Age (years)	59.66 ± 9.08	57.75 ± 10.06	>0.05
FBG (mg/dl)	207.62 ± 66.56	83.24 ± 7.74	<0.001
PPBG (mg/dl)	286.03± 67.84	122.19 ± 9.76	<0.001
T3 (nmol/l)	1.32 ± 0.43	1.72 ± 0.48	<0.001
T4 (nmol/l)	80.21 ± 31.88	117.10± 42.69	<0.001
TSH (nmol/l)	6.03 ± 4.49	3.53 ± 2.82	<0.001
*p <0.05 is significant, p <0.01 is highly significant, p >0.05 non-significant (NS), SD = Standard Deviation.			

Table 2: Comparison of thyroid profile in type 2 diabetic cases and non-diabetic controls.

Parameter	Cases (mean ± SD)	Controls (mean ± SD)	p value
T3 (nmol/l)	1.32 ± 0.43	1.72 ± 0.48	< 0.001
T4 (nmol/l)	80.21 ± 31.88	117.10 ± 42.69	<0.001
TSH (nmol/l)	6.03 ± 4.49	3.53 ± 2.82	<0.001

Mean value of T3 level observed in cases was 1.32±0.43 nmol/l and that observed in controls was 1.72±0.48 nmol/l. After comparing cases and controls mean by student unpaired t test, p value obtained was <0.001. This means low T3 level observed in cases than control was highly significant or difference observed in cases and controls for T3 levels was highly significant.

Mean T4 level observed in cases was 80.21±31.88 nmol/l and that observed in controls was 117.1±42.69 nmol/l. After comparing cases and control mean by student unpaired t test, p value obtained was <0.001. This means low T4 level observed in cases than controls was highly significant or difference observed in cases and controls for T4 level was highly significant.

Mean TSH level observed in cases was 6.06±4.49 µIU/ml and that observed in controls was 3.53±2.82 µIU/ml. After comparing cases and control mean by student unpaired t test, p value obtained was <0.001. This means high TSH level observed in cases than controls was highly significant or difference observed in cases and controls for TSH level was highly significant.

Table 3: Total thyroid dysfunction data according to type of thyroid dysfunction and gender in Type 2 diabetes mellitus cases and non-diabetic controls.

Type of thyroid dysfunction	Cases (100)			Controls (100)		
	Male	Female	Total	Male	Female	Total
Primary hypothyroidism	21	24	45	07	12	19
Subclinical hypothyroidism	04	05	09	04	06	10
Primary hyperthyroidism	00	01	01	00	00	00
Subclinical hyperthyroidism	00	01	01	01	00	01
Total	25	31	**56**	12	18	**30**

Table 4: Prevalence of hypothyroidism and hyperthyroidism among cases and controls.

Parameter	Diabetic cases (100)		Non-diabetic controls (100)	
	Number of cases	Prevalence in %	Number of controls	Prevalence in %
Euthyroid	44	44%	70	70%
Total Hypothyroidism	54	54%	29	29%
Total Hyperthyroidism	02	02%	01	01%
Total	100		100	

Discussion

In this comparative cross-sectional hospital based study in 100 type 2 diabetes mellitus as cases and 100 non-diabetic healthy subjects as controls, prevalence of total thyroid dysfunction obtained was 56% in cases and 30% in controls. Most predominant thyroid dysfunction observed in cases was hypothyroidism (54%) and that in controls was also hypothyroidism (29%). Prevalence of primary hypothyroidism, subclinical hypothyroidism, primary hyperthyroidism and subclinical hyperthyroidism in cases was 45%, 09%, 01% and 01% respectively in cases and 19%, 10%, 00% and 01% in controls. Thus, in this study, among thyroid dysfunction, primary hypothyroidism was most predominant and subclinical hypothyroidism was second most predominant in both cases and controls.

Prevalence of total thyroid dysfunction (56%) in cases observed in this study was less than that of Mukherjee S et al. [21] study in which prevalence of total thyroid dysfunction observed was 75%. In contrast, overall hypothyroidism (54%) in cases observed in this study was higher than that of Mukherjee S et al. [21] in which it was 48.33%. Prevalence of total thyroid dysfunction observed in Pasupathi P et al. [22], Demitrost L et al. [23], Vikhe VB et al. [6], Ghazali SM et al. [5], Singh G et al. [24], Manjunath SC et al. [25], Radaideh ARM et al. [26] and Imam Subekti et al. [27] was 45%, 31.02%, 30%, 29.7%, 29%, 16%, 12.5% and 9.9% respectively which was lower than that observed in this study (56%). Prevalence of overall hypothyroidism observed in Mukherjee S et al. [21], Vikhe VB et al. [6], Pasupathi P et al. [22], Manjunath SC et al. [25], Elebrashy et al. [28], Al-Geffari M et al. [29], Demitrost L et al. [23], Swami RM et al. [30] and Imam Subekti et al. [27] was 48.33%, 22%, 28%, 16%, 45.2%, 25.3%, 27.7%, 43.1% and 7.59% respectively, whereas in this study obtained 54% which was higher than these studies.

Prevalence of subclinical hypothyroidism observed in Mukherjee S et al. [21], Radaideh ARM et al. [26], Manjunath SC et al. [25], Elebrashy et al. [28], Al-Geffari M et al. [29], Furukawa S et al. [31], and Swami RM et al. [30] was 33.33%, 4.1%, 13%, 6.45%, 9.5%, 8.7% and 31.03 % respectively, whereas this study obtained 09% which was higher than that observed in Radaideh ARM et al. [26], Elebrashy et al. [28], and Furukawa S et al. [31] but it was lower than that observed in Mukherjee S et al. [21], Manjunath S et al. [25], Al-Geffari M et al. [29], and Swami RM et al. [30]. Prevalence of overt hypothyroidism observed in cases in Mukherjee S et al. [21], Manjunath SC et al. [25], Elebrashy et al. [28], and Swami RM et al. [30] was 15%, 3%, 38.7% and 12.06% respectively, whereas this study obtained 45% which is higher than these studies.

Prevalence of overall hyperthyroidism observed in cases of Mukherjee S et al. [21], Vikhe VB et al. [6], Pasupathi P et al. [22], Singh G et al. [24], Al-Geffari M et al. [29], and Demitrost L et al. [23] was 26.66%, 08%, 17%, 05%, 3.2% and 02% respectively, whereas this study obtained 02% which is similar to Demitrost et al. [23] study but lower than other studies described.

Compared to Indian and Chinese population, Indonesian population had lower proportion of hypothyroidism among diabetics. It can be caused by the high prevalence of iodine deficiency in China and India compared to Indonesian population. Explanation for variability in hypothyroidism prevalence in different diabetes populations can be made by several parameters such as adequacy of iodine intake which can affect the baseline thyroid status of population and presence of goiter, metabolic determinants like population glycemic achievement, metabolic syndrome, several

comorbidities which related to thyroid dysfunction, and in epidemiology perspective, the total prevalence of diabetes in population. In other words, studies about comorbidities of diabetes and thyroid dysfunction is population specific [27].

In T2DM patients, association of thyroid diseases is unexplained. It may be related to the older age of T2DM patients; as elderly people have increased risk of thyroid disease. It may also be related to the fact that some T2DM patients actually have type 1 DM with a very slow onset and hence, they have the same genetic predisposition toward autoimmune disease as patients with type 1 DM [26]. Insulin resistance is present in T2DM, hypothyroidism and hyperthyroidism. Insulin resistance present in both overt and subclinical hypothyroidism, may increase cardiovascular risk, especially when it is associated with other frequently associated risk factors such as hyperlipidemia and elevated blood pressure [32].

Conclusion

This study concluded with the finding that the prevalence of thyroid dysfunction (56%) in T2DM cases was significantly higher than nondiabetic controls (30%). Most predominant type of thyroid dysfunction observed in T2DM cases was hypothyroidism (54%) and in controls was also hypothyroidism (29%). So cases of T2DM should be screened for thyroid function.

Limitations of study: Study is done with small sample size.

Financial support and sponsorship: Nil

Declaration: Article has not been submitted/published in any other journal. Order of authorship as placed in Manuscript is final and accepted by all.

References

1. Neha Yadav, Sujata Singh, Smita Gupta, Saurabh Mishra, Krishna Singh. Correlation between glycaemic control and dyslipidemia in type 2 diabetes mellitus patient. Int J Basic Clin Pharmacol. 2019; 8(6): 1387-1392.
2. Sujaya Raghavendra, Tarun Kumar Datta, Tumbanatham A, K R Sethuraman, K Jayasingh, Nagababu Pyadala. Fasting and postprandial lipid profile in type 2 diabetes mellitus: A Comparative study. International Journal of Contemporary Medicine Surgery and Radiology. 2018; 3(1): 161-165.
3. Vinu vij, Pallavi Chitnis, Vijay Kumar Gupta. Evaluation of thyroid dysfunction among type 2 diabetic patients. Int J Pharm Bio Sci, 2012; 2(4):150-155.
4. Saraswati Pradipta, Heri Wibowo, Dante Saksono Harbuwono, Ekowati Rahajeng, Rahma Ayu Larasati, Rona Kartika. Distribution patterns and risk factors of dyslipidemia in patients with type 2 diabetes mellitus: a cross-sectional study in Bogor, Indonesia. International Journal of Applied Pharmaceutics 2020; 12(1): 5-8.
5. Ghazali S. M and Abbiyesuku F. M., Thyroid dysfunction in type 2 diabetics seen at the University College Hospital, Ibadan, Nigeria., Nig. J. Physiol. Sci. 25(December 2010); 173-179.
6. Vikram B Vikhe, Shubhangi A Kanitkar, Krunal K Tamakuwala, Anu N Gaikwad, Meenakshi Kalyan, Rajani R Agarwal. Thyroid dysfunction in patients with type 2 diabetes mellitus at tertiary care centre. National Journal of Medical Research 2013; 3(4): 377-380.
7. Stanley U. Ogbonna and Ignatius U. Ezeani. Risk factors of thyroid dysfunction in patients with type 2 diabetes mellitus. Front. Endocrinol. 2019; Volume 10. Article 440: Pages 8.
8. Ajay Kumar Das, Naved Ahmad, Akash Gupta. Dyslipidemia and hypothyroidism in population of East Medinipur, West Bengal. JMSCR 2014; 2(5): 1049-1053.
9. Amit Saxena, Pragati Kapoor, Shikha Saxena and A K Kapoor. Effect of levothyroxine therapy on dyslipidemia in hypothyroid patients. Internal Journal of Medical Update 2013 july; 8(2): 39-49.
10. Abilash Nair, C. Jayakumari, P.K. Jabbar, R.V. Jayakumar, Nishant Raizada, Anjana Gopi, Geena Susan George, and T.P. Seena. Prevalence and association of hypothyroidism in Indian patients with type 2 diabetes mellitus. Journal of Thyroid Research, 2018; Article ID 5386129: 7 pages.
11. Hussain A, Elmahdawi A M, Elzeraidi N, et al. The effects of dyslipidemia in Subclinical hypothyroidism. Cureus November 16, 2019; 11(11): e6173. Available from: DOI: 10.7759/cureus.6173.
12. Penugonda Anveetha, Kotikala Prabhakara Rao, Vamsi Krishna Chittimoju. Study of thyroid profile in patients with type 2 diabetes mellitus. Int J Pharm Bio Sci 2015; 5(1): 24-30.
13. Mirella Hage, Mira S. Zantout and Sami T. Azar., Thyroid Disorders and Diabetes Mellitus., Journal of Thyroid Research, 2011; Article ID 439463: 7 pages.
14. Das BKL, Prassan N, Ansari MF, Panday MF, Agrawal K, Niraula A., Dyslipidemic profile in type 2 diabetes mellitus: A Hospital-based study from Western Nepal. Journal of Biomedical Sciences 2020; 7(2): 64-70.
15. AG Unnikrishnan, Suganthi Kumaran. Basic consideration in Diabetes mellitus. In: Sandhya A Kamath ed, Siddharth N Shah ed, Milind Y Nadkar ed, Vikram Londhey ed, Ghan Shyam Pangtey ed, Falguni Parikh ed et al., API Textbook of Medicine. 11th edition, volume 1, Mumbai (India). The Association of Physicians of India, CBS Publishers and Distributors Pvt. Ltd., 2019; 812.

16. Roche Diagnostics GmbH, Cobas. Elecsys T3; The electrochemiluminescence immunoassay (ECLIA) for the in vitro quantitative determination of triiodothyronine (T3) in human serum and plasma for use on cobas e immunoassay analyzers. 11731360 122, 2019-08, V 26.0 English. Pages 1-4.
17. Roche Diagnostics GmbH, Cobas. Elecsys T4; The electrochemiluminescence immunoassay (ECLIA) for the in vitro quantitative determination of thyroxine in human serum and plasma. 12017709 122, 2019-02, V 21.0 English. Pages 1-4.
18. Roche Diagnostics GmbH, Cobas. Elecsys TSH; The electrochemiluminescence immunoassay (ECLIA) for the in vitro quantitative determination of thyrotropin (TSH) in human serum and plasma for use on cobas e immunoassay analyzers. 08429324 190, 2019-08, V 1.0 English. Pages 1-4.
19. David Y. Gaitonde, Kevin D. Rowley and Lori B. Sweeney. Hypothyroidism: An Update. American Family Physician, 2012; 86(3): 244-251.
20. Transasia Bio-Medicals Ltd., Erba Mannheim XL-System packs. Glucose reagent, GOD-POD; Diagnostic reagent for quantitative in vitro determination of glucose in human serum, plasma and urine. Kit literature pack code no. 120266, 121185. Revision no. 0-010719 GLU.
21. Mukherjee S, Datta S, Datta P, Mukherjee AK, Maisnam I. A study of prevalence of primary hypothyroidism in recently diagnosed type 2 diabetes mellitus in a tertiary care hospital. Int J Sci Rep 2015; 1(2): 105-112.
22. Pasupathi P, Bakthavathsalam G, Saravanan G and Sundaramoorthi R. Screening for thyroid dysfunction in the Diabetic/Non-diabetic Population. Thyroid Science 2008; 3(8): CLS1-6.
23. Demitrost L, Ranabir S. Thyroid dysfunction in type 2 diabetes mellitus: A retrospective study. Indian J Endocr Metab 2012; 16: S334-5.
24. Singh G, Gupta V, Sharma AK and Gupta N., frequency of thyroid dysfunction among diabetes in Punjabi population. An International Journal, 2011; 3(1): 74-77.
25. Manjunath SC, Krishnamurthy V, Puttaswami BK, Prabhu S, Vishwanathaiah PM. Prevalence of subclinical thyroid disorders in type 2 diabetes mellitus. Int J Med Public Health 2013; 3(4): 330-334.
26. Abdel-Rehman M. Radaideh, Mohamad K. Nusier, Fawaz L. Amari, Anwar E. Bateiha, Mohammed S. El-Khateeb, Abeer S. Naser, Kamel M. Ajlouni. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. Saudi Med J 2004; 25(8): 1046-1050.
27. Imam Subekti, Laurentius A. Pramono, Esthika Dewiasty, Dante S. Harbuwono. Thyroid dysfunction in type 2 diabetes mellitus patients. Acta Med Indones – Indones J Intern Med 2017; vol 49. Number 4: 314-323.
28. Ibrahim N Elebrashy, Amr El Meligi, Laila Rashed, Randa F Salam, Elham Youssef, Shaimaa A Fathy. Thyroid dysfunction among type 2 diabetic female Egyptian subjects. Dove Press Journal, Therapeutics and Clinical Risk Management 2016; 12: 1757-1762.
29. Al-Geffari M, Ahmad NA, Al-Sharqawi AH, Youssef AM, Al-Naqeb D and Al-Rubeaan K., Risk factors of thyroid dysfunction among type 2 diabetic patients in a highly diabetes mellitus prevalent society. International Journal of Endocrinology 2013; article ID 417920: 1-6.
30. Swami RM, Naveen Kumar, Srinivasa K, Manjunath GN, Prasad Byrav DS, Venkatesh G. Evaluation of hypothyroidism as a complication in type 2 diabetes mellitus. Biomedical Research 2012; 23(2): 170-172.
31. Furukawa S, Yamamoto S, Todo Y, Maruyama K, Miyake T, Ueda T et al. Association between subclinical hypothyroidism and diabetic nephropathy in patients with type 2 diabetes mellitus. Endocrine Journal 2014; 1-8.
32. Leonidas H Duntas, Jacques Orgiazzit and Georg Brabantt., The interface between thyroid and diabetes mellitus., Blackwell Publishing Ltd, Clinical Endocrinology 2011; 75, 1-9.