Association between Subclinical Hypothyroidism and Albuminuria in Patients with Type 2 Diabetes Mellitus: A Cross Sectional Study in Iran

Atousa Najmaldin[1], Solmaz Askari[2] and Majid Foroutan[1*]

[1]*Department of Internal Medicine, Semnan University of Medical Sciences, Semnan, Iran*
[2]*Department of Internal Medicine, Golestan University of Medical Sciences, Gorgan, Iran.*

Authors' contributions

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

ABSTRACT

Introduction: Studies have shown the association between subclinical hypothyroidism and type 2 diabetes. However, the common complications of type 2 diabetes, such as diabetic nephropathy and albuminuria with subclinical hypothyroidism, are not fully clear yet. This study thus aimed to determine the association between subclinical hypothyroidism and albuminuria in patients with type 2 diabetes mellitus.

Methods: This was a cross-sectional study, of 140 individuals diagnosed with type 2 diabetes mellitus (DM) admitted to the internal clinics of Kosar Hospital in Semnan, Iran in 2017-2018. The participants were selected, and were compared based on having 2 TSH levels above normal (>4.2 mIU/L) 3 months apart, as well as patients were divided to two groups including, subclinical hypothyroidism group (n=40) and euthyroid group (n=100) based on demographic information, laboratory information and indicators such as albuminuria, and urinary albumin-to-creatinine ratio (UACR).

Findings: The mean and standard deviation of UACR in patients with subclinical hypothyroidism were significantly higher than those of euthyroid patients (46.09 ± 27 9.27 vs. 3.94 ± 0.24 and P = 0.015, respectively). In patients with subclinical hypothyroidism, there was a statistically significant

_____

Corresponding author: E-mail: dr_forotan@yahoo.com;

and direct relationship between UACR values with primary TSH level (r = 0.555, P< 0.001) and UACR values with secondary TSH level (r = 0.563, P< 0.001).

Conclusion: Among type 2 DM patients, the rate of albuminuria in subclinical hypothyroidism group was significantly higher than that of euthyroid patients and with increasing initial and recurrent TSH levels, UACR values and consequently albuminuria increased.

1. INTRODUCTION

Diabetes mellitus (DM) is an important and very common group of disorders characterized by varying degrees of insulin resistance, impaired insulin secretion and increased glucose production, affecting more than 285 million people worldwide. Its prevalence is growing rapidly [1]. One of the main complications of microvascular diabetes is end-stage renal disease (ESRD), which has led to a significant increase in mortality in diabetic patients [2]. One of the hallmarks of diabetes is albuminuria, which results from a gradual decline in kidney function. When albuminuria occurs continuously, common interventions (such as quitting smoking, improving blood sugar, and controlling blood pressure) may not effectively prevent the progression of diabetes [3] .Therefore, identifying the risk factors for diabetes and monitoring its progression improves the effectiveness of treatment and reduces the economic burden of the disease [4]. On the other hand, some studies have shown that the prevalence of people with thyroid disorders is significantly higher in people with type 2 diabetes, and subclinical hypothyroidism can be an independent risk factor for albuminuria in people with type 2 diabetes [5].

Thyroid hormones play an important role in regulating renal growth, renal hemodynamics, glomerular filtration rate (GFR), and sodium and water homeostasis [6]. Subclinical hypothyroidism (SCH) is an asymptomatic stage of hypothyroidism defined by elevated serum thyrotropin levels and normal serum free thyroxine levels [7,8]. Research has shown that SCH may lead to renal dysfunction through decreased GFR as well as changes in cardiovascular function and disorders of the renin-angiotensin system [9,10]. Several clinical studies have reported that SCH is also associated with diabetes and microalbuminuria [8,11]. In addition, some prospective studies have shown that levothyroxine (LT4) treatment can significantly reduce urinary albumin to creatinine ratio (UAER) and has protective effects in all patients with diabetes and SCH [12,13].

Therefore, considering that the pathogenesis of albuminuria in endocrine disorders is one of the topics that needs further investigation, and given the evidence for the role of thyroid hormones in the course of this disease [5], this study aims to investigate the association between subclinical hypothyroidism and albuminuria in type 2 diabetic patients.

2. IMPLEMENTATION METHOD

2.1 Patients

In this cross-sectional study, all patients with known type 2 diabetes mellitus admitted to the internal clinics of Kosar Hospital in Semnan, Iran in the years 2017 to 2018 were studied. Confirmation of type 2 diabetes, according to the history, necessary examinations and tests, was done under the supervision of an endocrinologist. In this study, the criteria for diagnosing type 2 diabetes mellitus included fasting blood sugar ≥ 126 or 2-hour glucose ≥ 200 or random blood glucose ≥ 200 with symptoms of diabetes such as polydipsia and polyuria and weight loss, and hemoglobin A_{1c} ≥ .6.5.

Inclusion criteria included; no clinical signs and symptoms of thyroid disease including fatigue, weakness, dry skin, cold and face and swelling of the hands and feet, no laboratory signs of thyroid disease including elevated TSH level associated with decreased free T_4 levels, no history of drug treatment such as levothyroxine for thyroid disease, and 20 years of age at least. Exclusion criteria included certain diseases such as cancer, liver disorders, kidney disorders and chronic infections (urinary tract infections), hematuria, heart failure, febrile illness, severe hyperglycemia, severe hypertension, taking drugs that affect the thyroid test such as glucocorticoids, oral contraceptives and nonsteroidal anti-inflammatory drugs, neither smoking nor doing strenuous exercise.

The sample size required for this study, using the findings of the study of Yasuda et al [5], was considered to be 140 people using G Power software considering that the standard deviation of urinary albumin in patients with subclinical diabetes and hypothyroidism was 16.90. Finally, using the convenience sampling method, 140 patients out of those who met the inclusion criteria and did not meet the exclusion criteria entered the study.

2.2 Working Method

Initially, a written consent was given to the individuals to agree to enter this study, and after providing a description and importance of this study and giving a full explanation of the process of this project, it was completed and approved by the research unit of Kowsar Hospital, affiliated to Semnan University of Medical Sciences, Iran. After identifying the participants in this study, a demographic information checklist for all individuals, including age, body mass index, systolic and diastolic blood pressure, duration of diabetes, and type of diabetes treatment was recorded. Also, laboratory information such as fasting plasma glucose, lipid profile including total cholesterol and high and low density lipoprotein-cholesterol levels, triglycerides, visceral fat index, lipid accumulation product index, thyroid function tests including total T_4 and thyroid T3RU thyroid stimulating hormone (TSH) and urinary albumin to creatinine ratio (UACR) were measured in a random urine sample. The UACR index was calculated based on the division of random urinary albumin in milligrams by the amount of random urinary creatinine in grams. ELISA tests were performed to measure serum levels of TSH, T_4 Total and T3RU using Sunrise ELISA kit (Tecan, Co. Salzburg, Austria). In addition, if a urine sample was positive for microalbuminuria, first conditions that temporarily increase albumin excretion (including urinary tract infection, hematuria, strenuous exercise, febrile illness, heart failure, severe hypertension and severe hyperglycemia) were examined, and after rejecting these cases, the microalbuminuria test was repeated within 3 months. If the second test was positive, the diagnosis of microalbuminuria was proposed. Also, in this study, TSH (in people with high TSH) was checked twice to increase the accuracy of the measurement.

2.3 Evaluations of Patients

After completing the checklist of demographic, clinical and laboratory information, the subjects were divided into the following two groups based on TSH and total T_4 and T_3 RU levels and having 2 TSH levels above normal (>4.2 mIU/L) 3 months apart.

2.3.1 Subclinical hypothyroid group

Subject with type 2 DM + subclinical hypothyroidism (N=40)

2.3.2 Euthyroid group

Subject with type 2 DM without subclinical hypothyroidism (N=100)

In this study, the diagnostic criteria for subclinical hypothyroidism were high serum TSH concentration > 4.2 mIU/ L with normal serum FT_4 level. Then, laboratory indices and information, especially urinary albumin and UACR index in the two groups were examined and compared.

2.4 Statistical Analysis

Data were analyzed by SPSS statistical analysis software version 23. For numerical variables, standard deviation ± Mean were reported for statistical description while categorical variables were reported as proportion and percentage. In all tests, the confidence level was 95% and the significance level was less than 5%. Also, logistic regression analysis was performed in order to evaluate the simultaneous effect of different variables in this study on albuminuria (UACR).

3. RESULTS

In this study, 140 patients with known type 2 diabetes based on having 2 TSH levels above normal > 4.2 mIU/L were compared with interval 3 months in two groups with subclinical hypothyroidism (n=40) and without subclinical hypothyroidism (n=100).

In the present study, the mean and standard deviation of age in the two groups of patients with and without subclinical hypothyroidism were 61.23 ± 8.72 and 59.14 ± 10.41, respectively. Also, there was no significant difference between the ages of the two groups (P = 0.796). According to Table 1, most people in the group with subclinical hypothyroidism (60%) were in the elderly age group and most people in the group without subclinical hypothyroidism (47.0%) were in the middle age and elderly group. In terms of

sex, 67.5% (n=27) of the subjects with subclinical hypothyroidism and 59% (n=59) of the euthyroid group were female and the rest were male. Also, there was no significant difference between the sex of the two groups (P=0.602). Examining the duration of having diabetes also showed that the mean and standard deviation in the two groups were 10.18 ± 4.86 and 11.19 ± 12.95 years, respectively. There was no significant difference between the durations of having diabetes in the two groups (P=0.468).

BMI examination in patients showed that most of the subjects in both groups were overweight (Table 1). Also, the mean and standard deviation in the two groups were 27.77 ± 3.90 and 27.46 ± 3.23 kg/m^2, respectively, and no significant difference was observed between the two groups (P=0.589). Also, according to Table 1, there was no significant difference between the types of diabetes treatment in the two groups (P=0.452).

Laboratory data showed that the mean and standard deviation of fasting blood sugar levels in the two groups of subjects with and without subclinical hypothyroidism were 158.4 ± 45.42 and 156.1 ± 55.51 millimoles per liter, respectively. There was no significant difference between the two groups (P=0.645).

Mean and standard deviation of hemoglobin A1C level and systolic and diastolic blood pressure in the two groups showed that the hemoglobin level in the two groups was 8.19 ± 1.60 and 8.03 ± 1.80 g/dl, respectively, which there was no significant relationship between the two no group (P=0.639). Mean systolic and diastolic blood pressure in the group with subclinical hypothyroidism were 128.9 ± 15.13 and 78.63 ± 6.60 *mmHg*, respectively, and in the group without subclinical hypothyroidism were 129.1 ± 18.55 and 80.70 ± 7.69 *mmHg*, respectively, and there was no significant difference in systolic (P=0.092) and diastolic (P=0.466) blood pressure levels between the two groups.

Also, according to Table 2, the study of anthropometric indices in the subjects showed that there was no significant difference between any of the anthropometric indices in the two groups (P> 0.05). Examination of lipid profile also showed no significant difference between the two groups (P> 0.05) (Table 2).

In this study, the formula of waist circumference (in centimeters) minus 58 multiplied by

triglyceride (in nanomoles per liter) was used to evaluate the lipid accumulation product index. Our findings showed that the mean and standard deviation of the lipid accumulation product index in the two groups were 5749.9 ± 2388.2 and 6525.6 ± 3796.8 mg/dL , respectively, this index had no significant difference between the two groups (P=0.413). The following formula was used to measure visceral fat index.

Waist circumference (in centimeters) divided by 36.58 plus (BMI multiplied by 1.85) multiplied by (triglyceride multiplied by 0.81) multiplied by (HDL divided by 1.52) [14].

According to our results, the mean and standard deviation of visceral fat index in the two groups were 178488.4 ± 80804. (g) and 192788.3 ± 96961.3 (g), respectively, and this index was not significantly different between the two groups (P=0.460).

According to Table 2, the level of primary TSH in patients with subclinical hypothyroidism was significantly higher than those of euthyroid patients (6.25± 0.83 vs 3.28± 1.44, P <0.001). But there was no significant difference between T4 and T3RU indices in the two groups (P> 0.05).

Also, the results of Table 3 showed that there was no significant difference between the types of hypertension treatment in the two groups (P=0.697).

In this study, albuminuria was obtained through urinary albumin-to-creatinine ratio (UACR). The mean and standard deviation of UACR in patients with and without subclinical hypothyroidism were 46.09 ± 9.27 and 3.94 ± 0.24, respectively, with a significant difference between the two groups (P=0.015). Thus, it can be said that the rate of albuminuria in patients with subclinical hypothyroidism was significantly higher than that of euthyroid individuals. The results of Pearson correlation coefficient test also showed that in patients with subclinical hypothyroidism, there was a statistically significant and direct relationship between UACR values with primary TSH level (r=0.558 and P< 0.001) and UACR values with secondary TSH level (r=0.563 And P< 0.001). This means that with increasing primary and secondary TSH levels, UACR values consequently, albuminuria also increased, and vice versa.

4. DISCUSSION

Thyroid dysfunction and diabetes are two common diseases seen in the endocrine system. Studies have shown that the prevalence of thyroid disease, especially SCH, in patients with DM is significantly higher than healthy individuals [15,16].The results of our study showed that the two groups in terms of contextual or confounding variables such as age, sex, duration of diabetes, body mass index, anthropometric indices, current type of diabetes treatment, fasting blood sugar level, hemoglobin A1C level, systolic and diastolic blood pressure level, lipid profile, visceral and lipid accumulation product index were not significantly different and therefore, it was possible to better judge the results of the relationship between subclinical hypothyroidism and albuminuria in patients with type 2 diabetes mellitus with more precision by eliminating the effect of these variables [17]. According to the results of the present study, the rate of albuminuria in patients with subclinical hypothyroidism was significantly higher than that of euthyroid patients.

In a similar study, Yasuda et al. showed that the urine albumin to creatinine ratio in a random urine sample (UACR index) was significantly higher in patients with subclinical

Table 1. Demographic information of the subjects with type 2 diabetes in the two groups studied

Variables		With subclinical Hypothy roidism (N=40)		Euthyroid (N=100)	
		Number	Frequency percentage (%)	Number	Frequency percentage(%)
Age group	Young (20 to 39 years)	-	-	6	6.0
	Middle-aged (40 to 59 years old)	16	40.0	47	47.0
	Elderly (≥ 60 years old)	24	60.0	47	47.0
BMI	Normal (18.4 to 24.9)	2	5.0	15	15.0
	Weight gain (25 to 29.9	31	77.5	67	67.0
	Overweight (≥ 30)	7	17.5	18	18.0
Type of diabetes treatment	Insulin	20	50.0	43	43.0
	Oral medications	20	50.0	57	57.0

Table 2. Anthropometric indices and laboratory information in patients with type 2 diabetes mellitus in the two groups

Variables		With subclinical hypothyroidism (N=40)		Euthyroid (N=100)		P-value
		Mean	Std. Deviation	Mean	Std. Deviation	
Anthropometric indices	Height (cm)	168.5	8.56	166.4	10.34	0.079
	Weight (kg)	77.83	10.01	79.69	10.02	0.681
	Waist circum ference (cm)	96.28	8.96	96.51	7.65	0.204
Lipid profile (nanomoles per liter)	Triglyceride	152.2	66.0	166.7	86.28	0.324
	Total cholesterol	180.9	49.15	175.7	43.2	0.830
	LDL	95.13	35.26	94.91	36.77	0.311
	HDL	44.18	10.98	45.34	18.77	0.828
Thyroid function tests (mIU/ml)	Primary TSH	6.25	0.83	3.28	1.44	< 0.001
	Secondary TSH	6.05	0.78	-	-	-
	T4	8.52	2.57	8.06	3.00	0.462
	T3RU	29.27	4.21	30.09	2.44	0.457

Table 3. Evaluation of the type of hypertension treatment in the two groups

Type of hypertension treatment	With subclinical hypothyroidism (N=40)		Euthyroid (N=100)	
	Number	Frequency percentage(%)	Number	Frequency percentage (%)
ACEI	28	70.0	68	68.0
ARB	7	17.5	18	18.0
CCB	5	12.5	14	14.0
Total	40	100	100	100

hypothyroidism than in euthyroid patients. More specifically, the authors of this study concluded that subclinical hypothyroidism could be an independent risk factor for albuminuria in people with type 2 diabetes [5]. In another study, it was reported that patients with subclinical hypothyroidism have an endothelial dysfunction that may lead to an increase in the prevalence of nephropathy and, consequently, an increase in albuminuria [18]. Aljabri et al. in the study of the relationship between hypothyroidism and albuminuria in type 2 diabetic patients in Saudi patients showed that hypothyroidism was observed in 35.9% of the diabetic patients with albuminuria. They also reported that albuminuria was 1.8 times higher in people with hypothyroidism than in patients with euthyroidism. Morever, they reported that hypothyroidsm with albuminuria was more common in the seventh decade (32%). Hypothyroidsm was non significantly more prevalent in females in the sixth decade and male in the seventh decade [19]. Furukawa et al. also suggested that SCH may be independently associated with diabetic nephropathy in Japanese patients with type 2 diabetes [20].

In addition, in our study, the results of Pearson correlation coefficient test showed that in patients with subclinical hypothyroidism, there was a statistically significant and direct relationship between UACR values with primary and secondary TSH levels.. This confirms the important role of thyroid hormones in renal growth and function and, consequently, the role of hypothyroidism in renal filtration system disorder. There are various hypotheses to justify this relationship. In a study by Chen et al., reported that the chance of developing diabetic retinopathy in patients with subclinical hypothyroidism was 1.15 times that of patients without subclinical hypothyroidism and the chance of developing diabetic nephropathy in patients with subclinical hypothyroidism was 3.15

times that of patients without subclinical hypothyroidism [21]. Iglesias et al. also stated that thyroid hormones play an important role in the growth and development of renal cells as well as the physiology and function of these cells [22]. Other studies have shown that subclinical hypothyroidism can increase creatinine levels and ultimately decrease GFR [23,24]. Another hypothesis about the association between subclinical hypothyroidism and albuminuria is decreased cardiac output and increased peripheral vascular resistance in these patients [25,26]. Recent studies have shown that patients with subclinical hypothyroidism develop disorders in vascular endothelial structure through reduced endothelium-related vasodilation and nitric oxide disorders, leading to an increase in albuminuria and impaired renal function in these patients [27]. On the other hand, according to some studies, in patients with nephrotic syndrome, severe loss of thyroid hormone-binding proteins in the urine, including thyroxine-binding globulin, transthyretin and albumin, leads to a decrease in total T4 [28,29]. They also mentioned other mechanisms involved in the relationship between SCH and UACR in patients with type 2 diabetes, the relationship between hypothyroidism and insulin sensitivity, and impaired glucose tolerance, which reduce the ability of insulin to use glucose in muscles. Decreased regulation of glucose transporter protein also directly affects insulin degradation [30-32].

Therefore, it seems that hypothyroidism reduces vasodilation and in diabetic patients with nephrotic syndrome, by excreting proteins bound to thyroid hormone, it further reduces the level of thyroid hormone.

In general, according to previous studies, low levels of thyroid hormones can be present in patients with serious diseases, and it has been found that the extent of these changes is related to both the severity of the disease and the

survival of patients. In particular, low FT3 levels have been considered as an independent predictor of mortality in patients with chronic kidney disease [4,33,34]. These observations suggest that low levels of thyroid hormones may act as a biomarker of diabetes and indicate the patient's next prognosis.

Finally, because this study has recently been done, not only in Iran, but also in the world and on the other hand, the difference in the prevalence of one or more variables in different geographical areas for genetic, geographical and cultural reasons that are always considered by researchers in the field of health and medical, it had a number of limitations. There are many known and unknown factors in the study that may affect the association between subclinical hypothyroidism and albuminuria but it is certainly not possible to study all of these cases, especially the type of nutrition, genetics, and how to control metabolic disorders, and it will require further studies in a wider statistical population. Therefore, it is suggested that, with the design of specific interventions, study the effect of subclinical hypothyroidism treatment and, consequently, reduction of thyroid hormone levels as one of the treatment options, on reducing the incidence of albuminuria in patients with type 2 diabetes mellitus be studied in future studies. It is also suggested that, if conditions exist, cellular and molecular studies be conducted to identify the pathogenesis and causes of the association between subclinical hypothyroidism and albuminuria so that practitioners, while identifying this association, can have higher attention and accuracy in planning the treatment protocols.

5. CONCLUSION

The results of this study showed that the rate of albuminuria in patients with subclinical hypothyroidism was significantly higher than that of euthyroid patients. To be more precise, in patients with subclinical hypothyroidism, there was a statistically significant and direct relationship between UACR values with primary and secondary TSH levels. This means that with increasing primary and secondary TSH levels, UACR values and, consequently, albuminuria increased, and vice versa. The results of this study can remind the treatment staff that in diabetic patients with albuminuria, the level of thyroid hormones can also be measured.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ockrim ZD Yorston. Managing diabetic retinopathy. Bmj. 2010;341:c5400.
2. Tuttle KR. Diabetic kidney disease: A report from an ADA consensus conference. Am J Kidney Dis. 2014; 64(4):510-33.
3. Dounousi E. Improvements in the management of diabetic nephropathy. Rev Diabet Stud. 2015;12(1-2):119-33.
4. Wang J. Association between thyroid function and diabetic nephropathy in euthyroid subjects with type 2 diabetes mellitus: A cross-sectional study in China. Oncotarget. 2019;10(2):88-97.
5. Yasuda T. Subclinical hypothyroidism is independently associated with albuminuria in people with type 2 diabetes. Diabetes Res Clin Pract. 2011;94(3):e75-7.
6. Benvenga S. F Guarneri. Molecular mimicry and autoimmune thyroid disease. Rev Endocr Metab Disord. 2016;17(4): 485-498.

7. Peeters RP. Subclinical hypothyroidism. N Engl J Med. 2017;376(26):2556-2565.

8. El-Eshmawy MM. Subclinical hypo-thyroidism is independently associated with microalbuminuria in a cohort of prediabetic egyptian adults. Diabetes Metab J, 2013;37(6):450-7.

9. Vickers NJ. Animal communication: When I'm calling you, Will you answer too? Curr Biol. 2017; 27(14):R713-r715.

10. Uemura O. Influence of thyroid function on glomerular filtration rate and other estimates of kidney function in two pediatric patients. CEN Case Rep, 2018;7(1):169-173.

11. Jia F. Subclinical hypothyroidism and the associations with macrovascular complications and chronic kidney disease in patients with Type 2 diabetes. Diabet Med. 2015;32(8):1097-103.

12. Liu P. Can levothyroxine treatment reduce urinary albumin excretion rate in patients with early type 2 diabetic nephropathy and subclinical hypothyroidism? A randomized double-blind and placebo-controlled study. Curr Med Res Opin. 2015;31(12):2233-40.

13. Shin DH. Thyroid hormone replacement therapy attenuates the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism. Thyroid. 2013;23(6):654-61.

14. Nemoto M. Development of automatic visceral fat volume calculation software for CT volume data. Journal of obesity;2014.

15. Ozair M. Prevalence of thyroid disorders in North Indian Type 2 diabetic subjects: A cross sectional study. Diabetes Metab Syndr. 2018;12(3):301-304.

16. Fleiner HF. Prevalence of thyroid dysfunction in autoimmune and type 2 diabetes: The Population-based HUNT Study in Norway. J Clin Endocrinol Metab. 2016;101(2):669-77.

17. Yang JK. An association between subclinical hypothyroidism and sight-threatening diabetic retinopathy in type 2 diabetic patients. Diabetes Care. 2010;33(5):1018-20.

18. Wang J. Association between thyroid function and diabetic nephropathy in euthyroid subjects with type 2 diabetes mellitus: A cross-sectional study in China. Oncotarget, 2019;10(2):88.

19. Aljabri K. Association between Hypothyroidism and Albuminuria in Patients with Type 2 Diabetes Mellitus in Saudi Community based Hospital. A Retrospective Single Centre Study. Ann Med Medical Res. 2019;2:1019.

20. Furukawa, S. Association between subclinical hypothyroidism and diabetic nephropathy in patients with type 2 diabetes mellitus. Endocr J. 2014;61(10): 1011-8.

21. Chen H.S. Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. Diabet Med. 2007;24(12):1336-44.

22. Iglesias P, JJ Díez. Thyroid dysfunction and kidney disease. Eur J Endocrinol. 2009; 160(4): 503-15.

23. Sayari S, Z Molaei, Z Torabi, The relationship between subclinical hypothyroidism and serum levels of uric acid and creatinine in children aged 2-14 years. Ann Pediatr Endocrinol Metab. 2018;23(1):38-42.

24. Patil VP. Evaluation of renal function in subclinical hypothyroidism. J Lab Physicians. 2018;10(1):50-55.

25. Udovcic, M., et al., Hypothyroidism and the Heart. Methodist Debakey Cardiovasc J. 2017;13(2):55-59.

26. Chrysant SG. The current debate over treatment of subclinical hypothyroidism to prevent cardiovascular complications. Int J Clin Pract. 2020;74(7):e13499.

27. Ott C. Reduction in basal nitric oxide activity causes albuminuria. Diabetes. 2011;60(2):572-6.

28. Lo JC. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int. 2005;67(3):1047-52.

29. Chakravarthy V, S Ejaz. Thyroxine-Binding globulin deficiency, in StatPearls;2020.StatPearls Publishing. Copyright © 2020, StatPearls Publishing LLC. Treasure Island (FL).

30. Martinez B, RM Ortiz. Thyroid hormone regulation and insulin resistance: Insights from animals naturally adapted to fasting. Physiology (Bethesda), 2017;32(2):141-151.

31. Vyakaranam S. Study of insulin resistance in subclinical hypothyroidism. Int J Health Sci Res. 2014; 4(9):147-153.

32. Xie J. The longitudinal effect of subclinical hypothyroidism on urine microalbumin-to-urine creatinine ratio in patients with type 2

diabetes mellitus. BMC Endocr Disord. 2019;19(1):84.

33. Zoccali C. Low triiodothyronine and survival in end-stage renal disease. Kidney Int. 2006;70(3): 523-8.

34. Schultheiss UT. Thyroid function, renal events and mortality in chronic kidney disease patients: The german chronic kidney disease study. Clinical Kidney Journal; 2020.