A Study on the Relationship between Subclinical Hypothyroidism and Diabetic Retinopathy in Type 2 Diabetic Patients

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Abstract: Diabetic retinopathy is one of the most common microvascular complications and the leading cause of blindness in adults between 30 and 65 years of age worldwide. Also, unrecognized thyroid dysfunction may impair metabolic control and add to cardiovascular, and other chronic complication risk in diabetic patients**.** This study aimed to investigate the relationship between subclinical hypothyroidism and the development of retinopathy. The study was carried on 75 patients of newly diagnosed type 2 diabetes mellitus, normotensive, without any apparent vascular complications. Our patients were divided into two groups. Group I included 48 patients who were euthyroid (futher divided int sub-groups Ia with TSH level ≥2<4 µIu/ml and Ib with TSH ≥0.4<2 µIu/ml. , while group II included 27 patients who were found to have subclinical hypothyroidism. Fasting and postprandial plasma glucose, lipid profile, HBA1c, free T4, TSH and fundus examination were done to all patients. The obtained results revealed that diabetic retinopathy was associated with sub-clinical hypothyroidism, with statistical significant difference between group I and group II. When group I and group II compared, it was found that there had been significant difference in TSH level in different stages of diabetic retinopathy. In conclusion subclinical hypothyroidism is associated with diabetic retinopathy in type 2 diabetic patients. There is a positive correlation between level of TSH and stage of diabetic retinopathy in type 2 diabetics with subclinical hypothyroidism.

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Key words: Diabetic retinopathy, subclinical hypothyroidism, endothelial dysfunction.

1. Introduction

Diabetic retinopathy is one of the most common microvascular complications of DM, and the leading cause of blindness in adults between 30 and 65 years of age worldwide **(Frier et al., 2011).**

Common risk factors for the development / worsening of microvascular complications in diabetes include duration of diabetes, type of diabetes (proliferative disease in type 1 and maculopathy in type 2);poor glycemic control, hypertension , and dyslipidemia**(Gabriela, 2010).**

It has long been recognised that thyroid hormones have marked effects on glucose homeostasis. Glucose intolerance is associated with hyperthyroidism and hypothyroidism is characterised by insulin resistance **(Razvi et al., 2008).**

Sub-clinical hypothyroidism, the most prevalent form of thyroid diseases, is more common in females and in the elderly, it is defined as an asymptomatic state characterized by high serum thyrotropin (TSH>4 mU/l) with peripheral thyroid hormone concentrations within the laboratory reference ranges. Such abnormalities in thyroid function tests are very common in the population and have been extensively dealt with in textbooks and reviews **(Trbojević, 2008).**

There is insufficient evidence to recommend for or against screening for thyroid disease with thyroid function tests in high-risk patients, including elderly persons, postpartum women, and persons with Down syndrome, but recommendations may be made on other grounds, such as the higher prevalence of disease and the increased likelihood that symptoms of thyroid disease will be overlooked in these patients **(Kenneth and Michael, 2005).** The preferred test is measurement of thyroid-stimulating hormone (TSH) using a sensitive immunometric or similar assay, because of its superior sensitivity and specificity and measurement of free T4 at the same time **(Kadiyala et al., 2010)**.

SCH is a common endocrine disorder and has been reported to range from 4 to 10% in large general population screening surveys **(Cooper, 2001)** Patients with diabetes mellitus are at an increased risk of thyroid disease, The frequency of thyroid dysfunction in diabetic patients is higher than that of the general population and up to a third of patients with type-1 diabetes (T1DM) and 4–17% in type- 2 diabetic patients in previous studies. ultimately develop thyroid dysfunction. Unrecognized thyroid dysfunction may impair metabolic control and add to cardiovascular, and other chronic complication risk in diabetic patients **(Kadiyala et al., 2010).**

Symptoms of subclinical hypothyroidism are particularly insidious and often overshadowed by coexisting health problems, or the symptoms are attributed to aging. Certain static and changing symptoms have been identified as the highest indicators of hypothyroidism. Static symptoms

include constipation, hoarse voice, and deep voice. Changing symptoms include increased constipation, hoarser voice, feeling colder, having puffier eyes, and having weaker muscles. In general, symptoms associated with hypothyroidism are high in specificity but low in sensitivity. Therefore, the absence of a symptom does not rule out thyroid disease **(Capen et al., 2008)**.

This study aimed to investigate the relationship between SCH and the development of retinopathy as a chronic microvascular complication of type 2 diabetes mellitus.

2. Patients and methods

Seventy five patients with age between 39-65 years old with newly diagnosed type 2 diabetes mellitus, normotensive, without any apparent vascular complications were recruited from Internal Medicine Department, Tanta University Hospital between February and September 2011 prospectively.

Participants were subjected to thorough clinical examination and the following laboratory investigations:

1- Fasting and postprandial blood glucose
2- Glycated hemoglobin
3- Thyroid stimulating hormone (TSH) by ELISA method
4- Free thyroxine (FT4)
5- Total lipid profiles

Principle of TSH estimation:

This TSH enzyme linked immunosorbent assay (ELISA) applies a technique called a quantitative sandwich immunoassay. The microtiter plate provided in this kit has been pre-coated with a monoclonal antibody specific for TSH. Standards or samples are then added to the microtiter plate wells and TSH if present, will bind to the antibody pre-coated wells. In order to quantitatively determine the amount of TSH present in the sample, a standardized preparation of horseradish peroxidase (HRP)-conjugated polyclonal antibody, specific for TSH are added to each well to "sandwich" the TSH immobilized on the plate. The microtiter plate undergoes incubation, and then the wells are thoroughly washed to remove all unbound components. Next, a TMB (3,3',5,5' tetramethyl-benzidine) substrate solution is added to each well. The enzyme (HRP) and substrate are allowed to react over a short incubation period. Only those wells that contain TSH and enzyme-conjugated antibody will exhibit a change in colour. The enzyme substrate reaction is terminated by the addition of a sulphuric acid solution and the colour change is measured spectrophotometrically at a wavelength of 450 nm **(Morimoto and Inouye, 1997).**

Those with normal free thyroxine (FT4) and an increased TSH (≥4 μIU/ml) level were diagnosed with SCH. We further divided euthyroid type 2 diabetic patients into two subgroups (TSH: 2.0 to <4.0 vs. 0.4 to <2.0 μIU/ml) and compared the two based on a more stringent "normal" reference interval of TSH suggested by the National Health and Nutrition Examination Survey (NHANES) III (Hollowell et al. 2002).

Fluorescein angiography was performed to all cases using the TRC-50IX digital fundus camera (Topcon Corp., Tokyo, Japan). The severity of diabetic retinopathy was graded based on the international clinical diabetic retinopathy severity scale **(Wilkinson et al., 2003).**

3. Results

As shown in table (1); base line characteristics of group I and II (regarding AGE, SEX, HBA1c, LDL-C, HDL-C, triglycerides, fasting and post prandial plasma glucose) showed no statistical significant difference between both groups.

As shown in table (2); the following results were found:

Among the 23 patients included in sub-group Ia, 5 patients (22%) had no diabetic retinopathy while 18 patients (78%) had mild diabetic retinopathy. In sub-group Ib 20 patients (80%) out of 25 had no diabetic retinopathy while 5 patients (20%) had mild diabetic retinopathy. In group II, all patients had diabetic retinopathy with 15 patients (56%) with mild diabetic retinopathy, 7 patients (26%) with non Proliferative diabetic retinopathy (moderate) and 5 patients (18%) with Proliferative diabetic retinopathy. (Fig1)

Statistical analysis showed that diabetic retinopathy was associated with sub-clinical hypothyroidism, with statistical significant ($p<0.001$) difference between group I and group II ($X^2=52.366$ $^{chi\text{-}square}$).

Analysis of our data revealed that there was significant difference in TSH level in different stages of diabetic retinopathy. (Fig2)

Mean TSH in sub-group Ia was (3.11±0.780), in sub-group Ib was (1.25±0.451), and in group II it was (6.465±2.011).

When group I and group II compared, we found that there was significant ($p<0.001$) difference in TSH level in different stages of diabetic retinopathy (**f**=22.473^{ANOVA}), also there was significant ($p=0.021$) difference in TSH level in relation to the occurrence of diabetic retinopathy when sub-groups Ia and Ib compared. In the same way we found that there was significant ($p<0.001$) difference in TSH level in different stages of diabetic retinopathy when Ia&II compared and on comparison of Ib&II.

In group II, there was significant ($p<0.001$) difference in TSH level in relation to stages of

retinopathy within the group patients (**f**=18.877^{krouskal}).

In group II, this significant difference in TSH level in relation to stages of diabetic retinopathy was more evident in lower levels of TSH as the association between higher levels of TSH and proliferative diabetic retinopathy was statistically insignificant.

Table 1: Base line characteristics of sudied groups

		Group I 48	Group II 27	T-test	
				t	P-value
Age		43.546±11.890	46.52±9.51	1.114	0.2691
Sex N (%)	**F**	22(45.8%)	13(48.1%)	X^2 =0.017	0.896
	M	25(52.0%)	14(51.9%)		
LDL		2.942±0.721	3.12±0.8874	0.889	0.376
HDL		1.62±0.42	1.51±0.51	0.953	0.3438
TG		1.81±0.364	1.954±0.505	1.302	0.197
FPG		260.465±70.541	271.5±60.02	0.685	0.495
PPPG		275.65±55.61	280.66±71.45	0.337	0.7368
HbA1c		7.15±0.566	7.251±0.612	0.720	0.473

Table 2: Distribution of diabetic retinopathy among studied groups and subgroups

		Group Ia (23)	Group Ib (25)	Group II (27)	test	P-value
Retinopathy	**Negative**	5(21.7%)	20(80%)	0(0.0%)	X^2 =52.366 chi-square	<0.001*
	mild	18(78.2%)	5(20%)	15(55.6%)		
	Non Proliferative (moderate)	0(0.0%)	0(0.0%)	7(25.9%)		
	Proliferative	0(0.0%)	0(0.0%)	5(18.5%)		
TSH	**Range**	(2-4)	(0.4-2)	(4-10)	**f**=22.473 ANOVA	<0.001*
	Mean±SD	3.11±0.780	1.25±0.451	6.465±2.011	**Ia&Ib**=0.021* **Ia&II**<0.001* **Ib&II**<0.001*	
	mild			4.66±0.890	**f** =18.877 krouskal	<0.001*
	Non Proliferative (moderate)			6.213±1.19	P1<0.001* P2=0.031* P3=0.115	
	Proliferative			8.424±1.025		

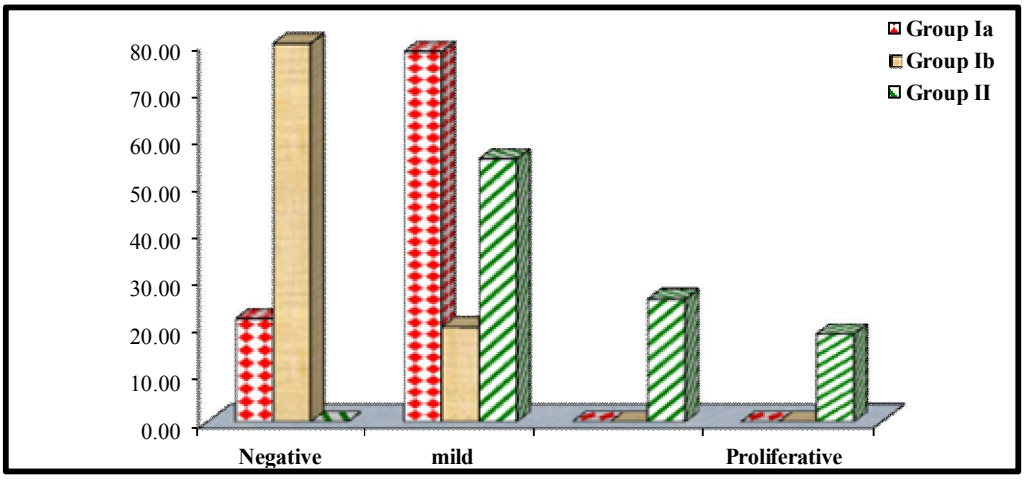

Fig1: Distribution of diabetic retinopathy among studied groups and subgroups

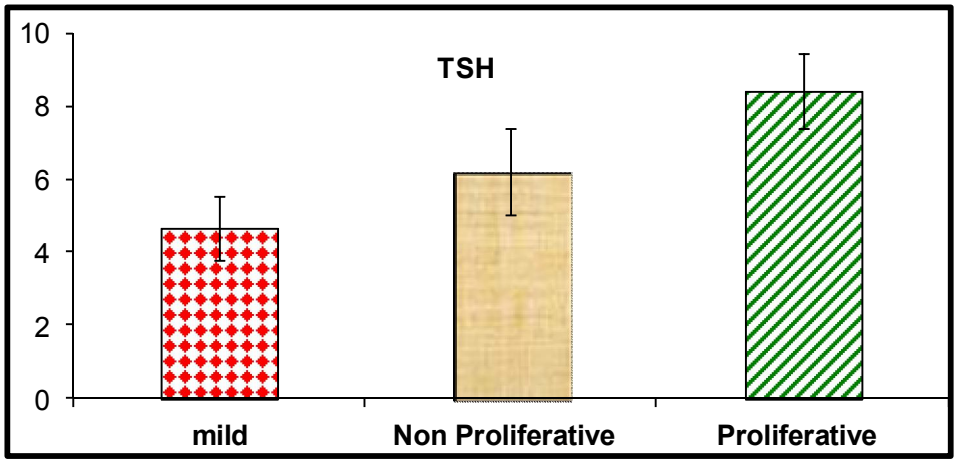

Fig 2: Grade of diabetic retinopathy in relation to TSH level

4. Discussion

Long term micro- and macrovascular complications represent the main cause of morbidity and mortality in both type 1 and type 2 diabetes. Microangiopathy is a common feature of both types of diabetes. The pathogenesis of diabetic vascular complications is complex and multifactorial. Early alterations of endothelial function may be involved in the development of microangiopathy in diabetic patients **(Kirpichnikov and Sowers, 2002).**

It is a very well known fact that the endothelium plays a major role in vascular tone, vascular homeostasis, vascular smooth muscle cell proliferation and thrombosis and thrombolysis balance through the production of a large number of vasoactive chemicals, growth modulators and other factors that mediate these functions **(Quyyumi, 1998).**

SCH has been reported to be associated with endothelial dysfunction independent from other well-known atherosclerotic risk factors **(Cikim, 2004).**

This study revealed significant association between SCH and diabetic retinopathy. Our findings are supported with the findings of **Yang et al., 2010,** who found that SCH was associated with diabetic retinopathy and sight threatening diabetic retinopathy (STDR).Another supporting report came from Korea as **Kim et al., 2011** stated that SCH was independently associated with severe diabetic retinopathy in patients with type 2 diabetes.

The mechanisms of developing diabetic retinopathy and diabetic nephropathy are similar and manifold. It was reported earlier that SCH was associated with higher prevalence of nephropathy in hospital based study **(Chen et al., 2007)** and diabetic patients with proteinuria had higher TSH level **(Gilles et al., 2008).**

Thyroid function contributes to normal retinal vascular density. Further, hypothyroidism can play a permissive role in the development of retinal neovascularization. Infants born very prematurely (27 weeks) were more likely to have low thyroxin levels indicating an abnormal function of hypothalamo- pituitary- thyroid axis **(Kristen, 2000).** Premature infants with low serum thyroxin were at risk of retinopathy of prematurity **(Fisher, 1990).** In addition hypothyroidism increased retinal vascular permeability in rats **(Tilton et al., 1989)**. Also; it was reported that methimazole- induced hypothyroidism in neonatal rats was associated with preretinal neovascularization **(Mookadam et al., 2004).**

Endothelial dysfunction in SCH could be due to inflammation. Acute and chronic inflammation is strongly related to endothelial dysfunction **(Hingorani et al., 2000).**

Furthermore higher levels of IL-6, TNF-alpha and high-sensitive C-reactive protein (hs-CRP) in patients with SCH were reported **(Türemen et al., 2011).** All of these inflammatory markers were correlated with endothelium-dependent vascular response which was lower in the patients of SCH. These findings show that there is low grade chronic inflammation in patients with SCH due to autoimmune thyroiditis and this inflammation may be one of the contributing factors that lead to endothelial dysfunction in patients with SCH **(Türemen et al., 2011)**.

Also; insulin resistance has been shown to be present in peripheral tissues in hypothyroid animal models **(Czech et al., 1980).** Similarly; insulin resistance in patients of subclinical hypothyroidism was concluded by **Maratou et al., 2010**.

Higher levels of fasting insulin, total cholesterol and LDL- C were reported in patients with subclinical hypothyroidism as compared with control group **(Al Sayed et al., 2006).**

Also, it was reported that the systolic and diastolic blood pressure and HOMA-IR values were higher in type 2 diabetic patients with SCH

than in type 2 diabetic euthyroid patients **(Kim et al., 2011).**

Also; higher serum levels of high-sensitive C-reactive protein, insulin, total cholesterol and LDL-C were found in patients with SCH compared to euthyroid subjects **(Tuzcu et al., 2005).**

Insulin resistance syndrome has characteristics of endocrine and metabolic disturbances along with inflammatory state **(Alexander et al., 2003).** These metabolic disturbances and inflammatory state may explain endothelial dysfunction in patients with SCH and yet explains the development of diabetic retinopathy.

In type 2 diabetes, there is a complex interaction between impaired insulin sensitivity, vascular endothelial dysfunction, and hypertension, which seems to play an important role in the development of functional disturbances in the microcirculation. Impaired insulin sensitivity is associated with a modification of arterial resistance and increased peripheral microvascular resistance, which contributes to the excessive prevalence of hypertension in type 2 diabetes. In these patients, an increased peripheral microvascular resistance occurs with even minor degrees of impaired glucose tolerance, which coexists with disturbed capillary pressure autoregulation, leading to the development of irreversible structural changes in the microvasculature **(Jaap et al., 1994).** Actually this complex interaction can be augmented in the presence of SCH.

Another possible factor which can cause endothelial dysfunction in patients with SCH is hyperlipidemia. It is a very well known fact that hyperlipidemia causes endothelial dysfunction per se by diminishing expression of endothelial nitric oxide synthase(eNOS) and by increasing asymmetric dimethylarginine levels, an eNOS endogenous inhibitor **(Ito et al.,1999).**

Our results showed that there was higher rate of diabetic retinopathy in euthyroid patients who had higher levels of TSH, with no cases of proliferative diabetic retinopathy. In the same way we found that type 2 diabetic patients with subclinical hypothyroidism had an association between TSH level and the grade of diabetic retinopathy.

Similar findings were reported by **YANG et al., 2010,** who found that euthyroid patients with higher levels of TSH demonstrated a higher rate of STDR than patients with lower levels.

In the same way; **Guang et al., 2010** reported that patients with higher levels of TSH had a significantly higher rate of PDR than patients with lower levels of TSH.

The new National Academy of Clinical Biochemistry (NACB) guidelines state that "greater than 95% of healthy, euthyroid subjects have a serum TSH concentration between 0.4- 2.5 μIU/ml" **(Baloch et al., 2003).** This newly advocated range of TSH for healthy euthyroid patients may explain the association between occurrence of diabetic retinopathy and TSH level in our group of type 2 diabetics with euthyroidism as well as the association between TSH level and the stage of diabetic retinopathy in type 2 diabetic patients with subclinical hypothyroidism.

The high incidence of diabetic retinopathy in our newly diagnosed type 2 diabetic Egyptian patients may be explained on the bases of negligence to seek medical advice by Egyptian patients coming from sub-urban regions and villages. Genetic differences can explain the difference of TSH level in relation to the development of PDR which is higher than found in the studies coming from China.

In conclusion; Subclinical hypothyroidism is associated with diabetic retinopathy in type 2 diabetic patients. There is also an association between level of TSH and the stage of diabetic retinopathy in type 2 diabetics with subclinical hypothyroidism.

We recommend screening for SCH in type 2 diabetic patients with diabetic retinopathy in attempt to correct SCH as a measure to combat progression of diabetic retinopathy.

Abbreviations:

FPG : fasting plasma glucucose
HBA1c : glycated hemoglobin
HDL-c : high density lipoprotein cholesterol
LDL-c : low density lipoprotein cholesterol
PPPG : postprandial plasma glucose
SCH : subclinical hypothyroidism
TG : triglycerides
TSH : thyroid stimulating hormone
hs- CRP: high-sensitive C-reactive protein
(STDR):sight threatening diabetic retinopathy

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References

1. Alexander, C. M.; Lendsman, P. B.; Teutsch, S. M.and Haffner, S. M. (2003): NCEP- defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes; 52: 1210-1214.
2. Al Sayed, A.; Al Ali, N.; Bo Abbas, Y. and Alfadali, E. (2006): Subclinical hypothyroidism is associated with early insulin resistance in Kuwaiti women. Endocrine Journal; 53 (5); 653-657.
3. Baloch, Z.; Carayon, P.; Conte- Devolx, B.; Demers, L. M.; Feldt- Rasmussen, U.; Henry, J. F.; Livosli, V. A.; Niccoli- Sire, P.; John, R.; Ruf, J.; Smyth, P. P.; Spencer, C. A. and Stockigt, J. R. (2003): Guidelines Committee, National Academy of Clinical Biochemistry Laboratory medicine practice

guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease.Thyroid; 13: 3-126.
4. Capen, C. (2008): Comparative anatomy and physiology. In The Thyroid. Braverman L, Utiger R, Eds. Philadelphia, Lippincott Williams & Wilkins; p. 20–24.
5. Chen, H. S.; Wu, T.E.; Jab, T.S.; Lu, R. A.; Wang, M. L.; Chen, R. L.and Lin, H. D. (2007): Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular disease in type 2 diabetic patients. Diabet. Med; 24: 1336-1344.
6. Cikim, A. S.; Oflaz, H.; Ozbey, N.; Cikim, K.; Umman, S.; Meric. M.; Sencer, E. and Molvalilar, S. (2004): Evaluation of endothelial function in subclinical hypothyroidism and subclinical hyperthyroidism. Thyroid; 14: 605-609.
7. Cooper, D. (2001): Subclinical hypothyroidism. N Engl J Med; 345:260–265.
8. Czech, M. P.; Malbon, C.C.; Kerman, K.; Gitomer, W. and Pilch, P.F. (1980): Effect of thyroid status on insulin action in rat adipocytes and skeletal muscle. Journal of Clinical Investigation; 66:574–582.
9. Fisher, D. A. (1990): Euthyroid low thyroxine (T4) and triiodothyronine (T3) states in premature and sick neonates. Pediatr. Cli. North Am; 37: 1297- 1312.
10. Frier, B. M. and Fisher, M. (2011): Diabetis Mellitus, In Davidson 21th ed), Nicki R, ColledgeBR, Walker S, et-al. Elsevier inc.: 805-849.
11. Gabriela Brenta (2010): Diabetes and thyroid disorders,Br J Diabetes Vasc Dis 2; 10: 172–177.
12. Gilles, R.; Den Hejier, M.; Ross, A. H.; Sweep, F. C.; Hermus, A.R.and Wetzels, J.F. (2008): Thyroid function in patients with proteinuria. Neth. J. Med; 66: 483-485.
13. Guang- Ran Yang, Jin- Kui Yang, Lin Zhang, Yan-Hua An and Jing- Kai Lu (2010): Association between subclinical hypothyroidism and proliferative diabetic retinopathy in type 2 diabetic patients: a case control study. Tohoku J. Exp. Med; 222: 303-310.
14. Hingorani, A. D.; Cross, J.; Kharbanda, R. K.; Mullen, M. J.; Bhagat, K.; Taylor, M.; Donald, A. E.; Palacios, M.; Griffin, G. E.; Deanfield, J. E.; MacAllister, R. J.and Vallance, P. (2000): Acute systemic inflammation impairs endothelium-dependent dilatation in humans. Circulation;102: 994-999.
15. Hollowell, J. G.; Staehling, N. W.; Flanders.W. D.; Hannon, W. H.; Gunter, E. W.; Spencer, C. A. and Braverman, L. E. (2002): Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Meta; 87: 489– 499.
16. Ito, A.; Tsao, P. S.; Adimoolam, S.; Kimoto, M.; Ogawa. T. and Cooke, J. P. (1999): Novel mechanism for endothelial dysfunction: dysregulation of dimethylarginine dimethylaminohydrolase. Circulation; 99:3092-3095.
17. Jaap, A. J.; Hammersley, M. S. and Shore, A.C. (1994): Reduced microvascular hyper-aemia in subjects at risk of developing type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia; 37: 214–16.
18. Kadiyala, R.; Peter, R. and Okosieme, O. E (2010): Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. Int J Clin Pract; 64(8):1130-9.
19. Kenneth, M. Shaw and Michael, H. Cummings (editors) (2005): Diabetes: Chronic Complications textbook, Wiley & Sons Ltd.: 1-20.
20. Kim, B.; Kim, C.; Jung, C.; Mok, J.; Suh, K. and Kang, S. (2011): Association between subclinical hypothyroidism and severe diabetic retinopathy in Korean patients with type 2 diabetes. Endocrine Journal; 58 (12):1065-1070.
21. Kirpichnikov, D. and Sowers, J. R. (2002): Diabetes mellitus and diabetes-associated vascular disease. Trends Endocrinol Metab.; 12: 225–230.
22. Kristen, D. (2000): The thyroid gland: physiology and patho physiology. Neonatal Netw; 19: 11-26.
23. Maratou, E.; Hadjidakis, D. J.; KolliaS, A.; Tsegka, k.; Peppa, M.; Alevizaki, M.; Mitrou, P.; Lambadiari, V.; Boutati, E.; Nikzas, D.; Tountas, N.; Economopoulos, T.; Raptis, S. A. and Dimitriadis, G. (2010): Studies of insulin resistance in patients with clinical and subclinical hyperthyroidism. European Journal of Endocrinol; 163(4):625–630.
24. Mookadam, M.; Leske, D. A.; Fautsch, M. P.; Lanier, W. L. and Holmes, J. M. (2004): The anti- thyroid drug metimazole induces neovascularization in the neonatal rat analogous to ROP. Invest. Ophthalmol. Vis. Sci; 45: 4145- 4150.
25. Morimoto, K. and Inouye, K. (1997): A sensitive enzyme immunoassay of human thyroid-stimulating hormone (TSH) using bispecific F(ab')2 fragments recognizing polymerized alkaline phosphatase and TSH. J Immunol Methods ;205(1): 81-90.
26. Quyyumi, A. (1998): Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. Am J Med; 105: 32S-39S.
27. Razvi, S.; Shakoor, A.; Vanderpump, M.; Weaver, J. U. and Pearce, S. H.(2008): The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. J Clin Endocrinol Metab; 93:2998–3007.
28. Tilton, R. G.; Pugliese, G.; Chang, K..; Speedy, A.; Province, M. A.; Kilo, C. and Williamson, J. R.(1989): Effects of hypothyroidism on vascular 1251- albumin permeation and blood flow in rats. Metabolism; 38: 471-478.
29. Trbojević, B. (2008): Subclinical thyroid disease--should we treat, should we screen for it? Article in Serbian, Srp Arh Celok Lek; 131(11-12):467-73.
30. Türemen, E. E.; Çetinarslan, B.; Şahin, T.; Cantürk , Z. and Tarkun, I (2011): Endothelial dysfunction and low grade chronic inflammation in subclinical hypothyroidism due to autoimmune thyroiditis. Endocrine Journal; 58 (5): 349-354.
31. Tuzcu, A.; Bahceci, M.; Gokalp, D.; Tuzun, Y. and Gunes, K. (2005): Subclinical hypothyroidism may be associated with elevated high- sensitive C- reactive protein (low grade inflammation) and fasting hyperinsulinemia. Endocrine Journal; 52 (1): 89- 94.
32. Wilkinson, C. P.; Ferris, F.L 3rd.; Klein, R. E.; Lee. P.P.; Agardh, C.D.; Davis. M.; Dills, D.; Kampik, A.; Pararajasegaram, R. and Verdaguer. J.T. (2003): The Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology; 110: 1677–1682.
33. YANG, J.; SHI, J.; LIU, W. and LI, Y. (2010): An association between subclinical hypothyroidism and sight threatening diabetic retinopathy in type 2 diabetic patients. Diabetes care; 5: 1018-1020.

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