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RESEARCH ARTICLE

THE IMPACT OF TSH LEVEL ON ALBUMINURIA AND GLOMERULAR FILTRATION RATE IN TYPE 2 DIABETES MELLITUS.

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Abstract

Purpose/Aim: Subclinical hypothyroidism (SCH) is common in patients with type 2 diabetes. The aim of this work is to investigate for the presence of an association between subclinical hypothyroidism and chronic kidney disease (CKD) in patients with type 2 diabetes mellitus. **Materials and Methods:** The study included 100 subjects with diabetes mellitus and normal serum creatinine from Kasr EL Ainy Hospital outpatient clinic of diabetes mellitus and endocrinology. TSH, FT4, urine albumin/creatinine ratio and eGFR were measured. Other diabetic complications were sought. A cut-off value of TSH 3.5 μ IU/L was used to define SCH.

Results: Twelve patients from the study cohort had SCH. Regression analysis indicated that higher TSH levels were associated higher A1c (regression coefficient \pm SE, 2.63 \pm 0.26), increased albuminuria (regression coefficient \pm SE, 15.45 \pm 3.03) and decreased eGFR (regression coefficient \pm SE, -31.89 \pm 3.20).

Conclusions: SCH patients have a higher risk for albuminuria and decreased eGFR, thus are at a higher risk for progression of diabetic nephropathy. This data highlights the importance of thyroxine replacement for even the smallest degrees of TSH elevation in patients with type 2 diabetes mellitus.

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Introduction:-

Subclinical hypothyroidism (SCH) represents an elevation of serum thyroid stimulating hormone (TSH) with normal serum thyroxine level. It is classically asymptomatic.[1] SCH is not uncommon in type 2 diabetes with a prevalence ranging from 2.2-17%. [2, 3] However, little research was done concerning the impact of SCH on microvascular complications of diabetes.[4]

Moreover, the precise cut-off level of SCH remains controversial. The NHANES study reported a normal TSH range (2.5th–97.5th percentile) of 0.45–4.12 μ IU/L.[5] Further analysis of this data, with adding longitudinal data proved that symptomatic thyroid disease can occur with TSH as low as 3.0 μ IU/L.[6] Indeed, the mean TSH levels in the normal population was reported as 1.18-1.40 mU/liter range. A normal individual is expected to have a TSH level less than 2.5 μ IU/L. This implies that higher TSH levels should be regarded carefully even if the cut-off level of normality is unclear, especially if comorbidities known to be affected by thyroid dysfunction are at stake.[7]

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Thyroid abnormalities can have a great impact on renal disease.[8] hypothyroidism is known to decrease sodium reabsorption by the kidney and to reduce renal blood flow.[9,10] Also, hypothyroidism is more prevalent in patients with impaired renal functions.[11] Patients with chronic kidney disease (CKD) who are euthyroid show better prognosis of renal disease as well as higher survival rates than those with inadequately controlled hypothyroidism.[12,13]

The aim of this work was to investigate for the presence of an association between subclinical hypothyroidism and chronic kidney disease (CKD) in patients with type 2 diabetes mellitus.

Materials and Methods:-

Patients were recruited from Endocrinology and Diabetes outpatient clinic, Kasr Al Ainy Hospital Cairo University during the period November 2013 to February 2014. All patients were known to have type 2 diabetes mellitus, about 50% were on insulin treatment and the rest on oral hypoglycaemic drugs, all on regular follow up. Patients were consecutively enrolled into the study as long as they were 35-50 years old and with disease duration no more than 15 years, and had a normal range serum creatinine.

A written informed consent was obtained from all patients. Patients with known thyroid illness or clinically detected goiters were excluded from the study. Patients were screened for subclinical hypothyroidism by measuring serum TSH and free T4.

Laboratory Workup:-

The following labs were done to all patients:

Lipid profile; triglycerides and total cholesterol by enzymatic colorimetric method and HDL by direct method in homogeneous phase, LDL was calculated by using the Friedewald formula), fasting plasma glucose level was measured by glucose oxidase method, serum creatinine was measured by kinetic colorimetric assay, HbA1c was analyzed on Dimension (Siemens) based on a turbidimetric inhibition immunoassay (TINIA) principle, serum level of TSH and fT4 were analyzed on Cobas e411 (Roche) based on Electrochemiluminescence immunoassay, microalbumin / creatinine ratio (random urine sample) was analyzed using Bio systems kit based on latex turbidimetry.

Patients with overt hypothyroidism (with decreased free T4) were treated accordingly and excluded from the study. Patients with a decreased TSH beyond the normal range with any thyroid function pattern were excluded. The CKD-EPI creatinine equation was used to estimate eGFR. [14]

TSH was treated as a continuous and categorical variable, which allowed for the comparison of the absolute amount of TSH to outcome variables as well as the comparison of outcome variables between SCH and non-SCH patients. Serum TSH was categorised as less than or "more than or equal to" 3.5 μ IU/L to classify SCH, according to the variations in the TSH upper limit recommendation.[7]

Statistics:-

Analysis of data was done using SPSS (statistical program for social science version 12) as follows:

Quantitative variables are expressed in mean \pm SD. Qualitative variables were expressed as number and percentage. Chi-square test was used to compare qualitative variables between groups. Unpaired t-test was used to compare quantitative variables, in parametric data ($SD < 50\%$ mean). P value < 0.05 was considered as significant. Univariate linear regression was used to test the effect of TSH as a continuous variable on A1c, A/C ratio and eGFR. A backward multivariable regression model was done to test the effect of various factors on albuminuria and eGFR.

Results:-

According to the selected criterion in this study, 88 patients were found to be euthyroid and 12 patients were found to have SCH. FT4 values among patients with SCH ranged from 0.72 - 1.50 ng/dl, with mean \pm SD, 1.12 ± 0.25 ng/dl. There was no difference in demographic data between the euthyroid group and those with SCH. The mean age was around 48 years for both groups (euthyroid group 48.4 ± 6.8 years and in SCH 48.6 ± 5.1 years, $P=0.857$). The duration of diabetes mellitus was also similar between the two groups, with the mean 8-9 years (euthyroid group 8.01 ± 3.518 and in SCH 9.67 ± 4.559 , $P=0.312$). The study cohort included 80 female and 20 male patients. The percentage of female subjects in euthyroid group was 81.8% and in SCH 66.7%, $P=0.194$.

BMI was greater in the group with SCH ($37.2 \pm 12.79 \text{ kg/m}^2$) than euthyroid group ($35.0 \pm 9.25 \text{ kg/m}^2$), this difference was not significant ($P=0.928$).

As regards glucose control, both groups were poorly controlled, especially the euthyroid group. FBS was more or less similar between both groups (euthyroid group $211 \pm 108 \text{ mg/dl}$ and in SCH $221 \pm 112 \text{ mg/dl}$, $P=0.657$). However, mean HbA1c was higher in euthyroid group ($9.5 \pm 1.75\%$) versus SCH group ($8.7 \pm 2.05\%$), $P=0.118$. There was no difference in lipid profile between the euthyroid group and those with SCH. The mean \pm SD of serum triglycerides (TG) was $182.52 \pm 140.56 \text{ mg/dl}$ in the euthyroid group and $181.17 \pm 89.44 \text{ mg/dl}$ in SCH, $P=0.671$. The mean \pm SD of serum low density lipoproteins (LDL) was $142.81 \pm 44.40 \text{ mg/dl}$ in the euthyroid group and $136.47 \pm 40.62 \text{ mg/dl}$ in SCH, $P=0.681$. The mean \pm SD of serum high density lipoproteins (HDL) was $37.98 \pm 9.17 \text{ mg/dl}$ in the euthyroid group and $40.42 \pm 9.95 \text{ mg/dl}$ in SCH, $P=0.353$.

Serum creatinine was significantly higher in the SCH group ($0.98 \pm 1.91 \text{ mg/dl}$) than euthyroid group ($0.65 \pm 0.23 \text{ mg/dl}$), $P=0.004$. However, HbA1c, ACR and eGFR were not significantly different in both groups (Table 1). Univariate regression analysis, however, showed a significant association of TSH as a continuous independent variable with all three dependent variables: HbA1c, eGFR and ACR. Regression coefficients and P values are shown in Table 2.

A multivariable regression model was done to test the effect of gender, age, duration of diabetes, BMI, type of treatment, serum creatinine, FBS, HbA1c, TSH, TG, LDL and HDL on albuminuria and eGFR. No significant associations were found.

Discussion:-

SCH is an everlasting hot topic concerning determination of cut-off points for diagnosis and treatment. This study is an important extension to the ongoing research aiming at disease-specific individualisation of SCH diagnosis and treatment. This approach best addresses cost-effectiveness of SCH correction in relation to associated risks implicated by the condition. In this study, the increased risk of chronic renal disease (CKD) with SCH was sought in patients with type 2 diabetes mellitus.

The triad of increased serum creatinine, higher ACR and decreased eGFR was proven to be more frequent in patients with SCH as compared to euthyroid counterparts with type 2 diabetes in this study. In stages 2 and 3 of diabetic nephropathy, the GFR is elevated, and there is no rise in creatinine. Rising creatinine signifies a fall in GFR, which heralds the progression to stage 4 and ESRD.[15] This means that SCH may be an important factor in progression of diabetic nephropathy.

Although the measurement of albuminuria is the cornerstone for the diagnosis of diabetic nephropathy, there are some patients with either type 1 or type 2 diabetes who have decreased glomerular filtration rate (GFR) in the presence of normal urinary albumin excretion. For patients with type 2 diabetes in NHANES III (Third National Health and Nutrition Examination Survey; $n=1,197$), low GFR ($<60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) was present in 30% of patients in the absence of micro- or macroalbuminuria and retinopathy. Although renal biopsy was not performed, this observation was probably related to renal parenchymal disease other than classical diabetic glomerulosclerosis. These studies indicate that normoalbuminuria does not protect from a decrease in GFR in type 1 and type 2 diabetic patients. Therefore, GFR should be routinely estimated and albuminuria routinely measured for a proper screening of diabetic nephropathy. [15]

This data suggest that the effect of SCH on diabetic nephropathy is not only exerted by increasing the severity of microalbuminuria or macroalbuminuria, but also by hastening the direct progression to stage 4. Review of previous studies in this field revealed a significant negative correlation between eGFR and TSH [16,17], a strong association between CKD and SCH [17-21], with increased prevalence of renal disease in SCH patients [17] in general.

However, besides a Japanese study done in 2014 with very similar results, no study has investigated the association between SCH and eGFR among patients with type 2 diabetes mellitus. In the latter study, SCH was not found to be an independent risk factor for CKD, but eGFR was lower in the SCH group than the euthyroid group.[22] This association between SCH and worsening renal function in patients with diabetic nephropathy highlights the importance of thyroxine replacement in such patients. A mouse model done in 2011 seemed promising.[23]

Levothyroxine replacement was shown to preserve renal functions and independently predict renal outcome in 309 patients with stage 2–4 chronic kidney disease and SCH. [24] Another study showed that thyroid replacement therapy may slow down the deterioration of eGFR in a cohort of patients, 39% of which had diabetes mellitus. [25]

Limitations:-

The relatively small number of SCH subgroup (n=12) as compared with the euthyroid group (n=88), made it difficult to obtain significant results by multivariable analysis.

Table 1:- TSH, A1c%, ACR and eGFR in euthyroid and SCH groups with Type 2 diabetes

	HBA1C /%		Albumin/Creatinine ratio/ $\mu\text{g}/\text{mg}$		eGFR /mL/min/1.73 m ²		TSH mIU/L	
SCH	present	absent	present	absent	present	absent	present	absent
Number	12	88	12	88	12	88	12	88
Mean	8.73	9.46	55.67	52.53	100.75	116.52	5.84	1.41
SD	2.05	1.76	55.75	72.68	35.70	22.90	2.27	0.63
Minimum	6.30	5.30	3.00	2.00	16.00	30.00	3.50	0.20
Maximum	13.20	13.40	163.00	487.00	165.00	163.00	10.80	3.10
P value*	0.1862		0.8862		0.1625		<0.0001	

SCH subclinical hypothyroidism; SD standard deviation

*P < 0.05 is significant; P > 0.05 is not significant

Table 2:- Regression of TSH against dependent variables

	HBA1C	ACR	GFR
Coefficient	2.63	15.45	-31.89
Standard Error	0.26	3.03	3.20
95% CI	2.12 to 3.14	9.44 to 21.46	-25.53 to -38.24
P value*	<0.0001	<0.0001	<0.0001

CI confidence interval

*P < 0.05 is significant; P > 0.05 is not significant

Conclusions and recommendations:-

Increased TSH was significantly associated with increased serum creatinine, increased ACR and decreased eGFR. SCH is thus regarded as a risk factor for diabetic nephropathy.

In view of the results of this study, the authors recommend that thyroid function screening should be added to routine follow-up of patients with type 2 diabetes mellitus. The cut-off for thyroid dysfunction in this subset of patients may fall to 3.5 $\mu\text{IU}/\text{L}$, if not lower. Levothyroxine replacement has to be carefully considered in such patients especially if eGFR was affected. Needless to point out, eGFR should be added to routine screening of diabetic nephropathy.

Further research:-

Further studies should include prospective studies to test for the possible effect of thyroxine replacement on SCH patients as regards complications of diabetes.

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Declaration of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References:-

1. Col NF, Surks MI, Daniels GH. Subclinical thyroid disease: clinical applications. *JAMA* 2004;291:239–43
2. Smithson, M.J. (1998) Screening for thyroid dysfunction in a community population of diabetic patients. *Diabet. Med.*, 15, 148-150.
3. Hak AE, Pols HA, Visser TJ, Drexhage HA, et al. (2000). Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Annals of Internal Medicine* 132(4):270-8
4. Yang J-K, Liu W, Shi J, Li Y-B. An Association Between Subclinical Hypothyroidism and Sight-Threatening Diabetic Retinopathy in Type 2 Diabetic Patients. *Diabetes Care*. 2010;33(5):1018-1020. doi:10.2337/dc09-1784
5. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. *J Clin Endocrinol Metab* 2005;90:5489–96
6. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab* 2005;90:5483–8
7. Hollowell JG, Staehling NW, Flanders WD, Gunter EW, Spencer CA, Braverman LE 2002 Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 87:489–499
8. Klein I, Danzi S 2007 Thyroid disease and the heart. *Circulation* 116:1725–1735
9. Iglesias P, Díez JJ 2009 Thyroid dysfunction and kidney disease. *Eur J Endocrinol* 160:503–515
10. Mariani LH, Berns JS 2012 The renal manifestations of thyroid disease. *J Am Soc Nephrol* 23:22–26
11. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int* 2005;67:1047–52.
12. Rhee CM, Alexander EK, Bhan I, Brunelli SM. Hypothyroidism and mortality among dialysis patients. *Clin J Am Soc Nephrol* 2013;8:593–601.
13. Shin DH, Lee MJ, Kim SJ, Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* 2012;97:2732
14. AS, Stevens LA, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2009; 150:604-612
15. Jorge L. Gross, Mirela J. de Azevedo, Sandra P. Silveiro, et al: Diabetic Nephropathy: Diagnosis, Prevention, and Treatment. *Diabetes Care* 28:164-176, 2005
16. Saini V, Yadav A, Arora MK, Arora S, Singh R, et al. (2012) Correlation of creatinine with TSH levels in overt hypothyroidism - a requirement for monitor- 1018 Furukawa et al. ing of renal function in hypothyroid patients? *Clin Biochem* 45: 212-4.
17. Asvold BO, Bjørø T, Vatten LJ (2011) Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study. *Eur J Endocrinol* 164:101-5.
18. KONG Yan-hua, REN An, WANG Ya-hong: The changes of renal function in diabetic patients with subclinical hypothyroidism. *China Journal of Modern Medicine* 24, 2011
19. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, et al. (2008) Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 3:1296-1300.
20. Lo JC, Chertow GM, Go AS, Hsu CY (2005) Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int* 67:1047-1052.
21. Chen HS, Wu TE, Jap TS, Lu RA, Wang ML, et al. (2007) Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. *Diabet Med* 24:1336-1344.
22. Shinya Furukawa, Shin Yamamoto, Yasuhiko Todo, Kotatsu Maruyama, Teruki Miyake, et al. Association between subclinical hypothyroidism and diabetic nephropathy in patients with type 2 diabetes mellitus. *Endocrine Journal* 2014, 61 (10), 1011-1018
23. Yi Lin and Zhongjie Sun: Thyroid hormone ameliorates diabetic nephropathy in a mouse model of type II diabetes *J Endocrinol* 209 (2) 185-191, 2011
24. Dong Ho Shin, Mi Jung Lee, Seung Jun Kim, et al . Preservation of Renal Function by Thyroid Hormone Replacement Therapy in Chronic Kidney Disease Patients with Subclinical Hypothyroidism. *J Clinical Endo Metabolism* 2012; 97(8): 2732-2740
25. Shin DH, Lee MJ, Lee HS, Oh HJ, Ko KI, et al. (2013) Thyroid hormone replacement therapy attenuates the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism. *Thyroid* 23:654-661.