PROPORTION OF SUB-CLINICAL HYPOTHYROIDISM AMONG PERSONS WITH DIABETES MELLITUS.

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Source/S Of Support: ICMR-STS
Word Count Of Main Text: 2118
Number Of Tables: 7
Number Of Figures: Nil
Number Of References: 24
Conflict Of Interest: None

ABSTRACT

Background*: Subclinical hypothyroidism is the most common abnormality involving the thyroid gland, affecting 3-16% of the people. It has a probability of progression to Overt Hypothyroidism which has many complications involving neurological and cardiovascular systems.* ***Objectives:*** *1) To study the proportion of sub-clinical hypothyroidism in diabetic persons 2) Factors associated with sub-clinical hypothyroidism in diabetic persons.* ***Methodology****: A Hospital based exploratory study was done on 155 persons with diabetes mellitus. The patients were selected from the Medicine and Endocrinology outpatient departments of K.R Hospital, Mysore. The information was gathered using a questionnaire after obtaining informed consent. Blood samples were taken to assess FBS, PPBS and thyroid profile.*

***Results**: The proportion of Subclinical Hypothyroidism was found to be 18%. Duration of diabetes was found to be significantly associated with higher proportion of Subclinical Hypothyroidism at 5% level of significance. The proportion showed increasing trend among females and increasing age with maximum proportion among persons above 60 years of age, but was insignificant. There is a significant proportion of Subclinical Hypothyroidism among individuals having Diabetes Mellitus. **Conclusion**: Regular screening for thyroid abnormalities in all diabetic patients will allow early treatment of subclinical thyroid dysfunction.*

KEY WORDS: *Subclinical hypothyroidism, diabetes mellitus*

INTRODUCTION

The number of people with type 2 DM is increasing in every country[1]. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world"[2].Diabetes Mellitus is a chronic, non communicable disease due to a group of common metabolic disorders, sharing the phenotype of hyperglycemia. In 2012 it has been estimated that about 371 million people have diabetes globally. More than 70.3 million people in the South East Asia Region have diabetes (of which 63 million is from India) [3]. Subclinical hypothyroidism (ScHt) is defined as high serum TSH concentration with normal serum Free Thyroxine (FT4) and Free Triiodothyronine (FT3) concentrations, associated with few or no signs and symptoms of hypothyroidism[4]. It is referred to as a state of mild thyroid failure and is essentially a laboratory diagnosis.

Subclinical hypothyroidism is the most prevalent thyroid disorder affecting 3–15%[5] of adult population. Prevalence increases with advanced age [6-8] female gender,[7,9] and greater dietary iodine intake[10,11]. Sub-clinical hypothyroidism is found in 6-8% of women(10% over age of 60 years) and 3% of men. The annual risk of developing clinical hypothyroidism is about 4% when sub-clinical hypothyroidism is associated with positive TPO antibodies[12,13].

Sub-clinical hypothyroidism may be risk factor for cardiovascular disease, decreases myocardial contractility and pulse rate, hence stroke volume and may be associated with

increased risk of coronary artery disease(CAD) and peripheral vascular disease[14-16].Glycemic status influences the T3 levels, basal TSH levels and TSH response to TRH [17].

Poorly controlled Type 1 and 2 diabetes, may induce a "Low T3 state",increase in reverse T3(rT3) but near normal serum T4 and TSH concentrations[18].

Low serum T3 is due to reduced peripheral conversion of thyroxine (T4) to triiodothyronine (T3) via 5' monodeiodination reaction. Poorly controlled diabetes may also result in impaired TSH response to TRH or loss of normal nocturnal TSH peak.

No significant information was available regarding this topic as, not many studies have been done in the southern part of Karnataka. So, this study aimed at filling the lacuna that exists in our understanding of subclinical hypothyroidism in diabetes in south Indian cities like Mysore. Hence, the present study has been done with following aims and objectives.

OBJECTIVES

1. To study the proportion of sub-clinical hypothyroidism in diabetic persons
2. Factors associated with sub-clinical hypothyroidism in diabetic persons

MATERIAL AND METHODS

This descriptive study was conducted in the Biochemistry, Endocrinology and General Medicine Departments of K.R.Hospital, Mysore Medical College & Research Institute, Mysore, from 01.05.2014 to 31.08.2014. The study was approved by institutional ethical committee and informed consent was taken from all subjects. Data was collected from 155 diabetic study subjects.

Inclusion Criteria:

Patients diagnosed with Diabetes ,Persons aged ≥ 18 years, Duration of Diabetes >1 year were included for the study

Exclusion Criteria:

Pregnant Women, Patients with recent interventions: Pulse Corticosteroids/ Radio-iodine/ History of hospitalization in the last 6 months, Persons already affected and being treated for thyroid disorder were excluded from the study.

First sample of 5ml of blood was drawn under aseptic condition with overnight fasting to assess FBS and Thyroid profile (T3,T4 and TSH) . A second sample of post-prandial blood of 2 ml was taken for the assessment of PPBS.

Criteria for diagnosis of Subclinical Hypothyroidism:

A raised value of TSH above the normal range with T3 and T4 being in the normal range was considered to be a case of subclinical hypothyroidism. The reference values are, respectively, 4.5 -11.5ug/dLfor T4; 75 -200ng/dL for T3; 0.27-4.20 μUI/ml for TSH. **Data Entry and Statistical Analysis:** The collected data was entered into Microsoft excel sheet and analysed using the SPSS software. Descriptive analysis was done by calculating proportion, mean and standard deviation for various characteristics. Inferential statistics was done by using Chi- square test.

OBSERVATION AND RESULTS:

Table 1: Age group distribution of study subjects

Age Group (Years)	Frequency	Percentage
21-40	37	23.9%
41-60	86	55.5%
61-80	32	20.6
TOTAL	155	100%

Table 2: Gender of study subjects

Gender	Frequency	Percent
Male	103	66.5%
Female	52	33.5%

Total	155	100%

Table 3: Thyroid profile of study subjects

Profile	**Frequency**	**Percentage**
Hypothyroid	9	5.806 %
Subclinical-Hypothyroid	28	18.064 %
Euthyroid(Normal)	112	72.258 %
Hyperthyroid	6	3.871 %
Total	155	100

Among the total study subjects, majority (55.5%) were in the age group of 40-60 years, majority (66.5%) were females. Most of the study subjects (53.9%) had their diabetes diagnosed in the last 5 years. 23.9% of the patients had hypertension and 6.5% people gave history of tuberculosis.Of the 155 people assessed, majority (72.25%) were euthyroid, followed by people having subclinical hypothyroidism (18.06%).

Table 4: Mean values of the parameters of study population.

Parameter	**MEAN± SD**
Age	49.97±11.85
Duration of diabetes	8.27±7.39
FBS	132.28±62.59
PPBS	208.75±95.61
T3	122.45±72.08
T4	8.63±3.47

TSH	4.34±8.42

The mean age of the study subjects was 50 years with a standard deviation of 11 years. Mean duration of diabetes was 8 years with a standard deviation of 7 years. Mean FBS and PPBS were in the higher range. Mean T3 and T4 lie under the normal range where as the mean TSH level exceeded the normal range.

Table 5: Association between thyroid profile and age of study subjects

Age Group	**Hypothyroidism**	**Subclinical Hypothyroidism**	**Normal**	**Hyperthyroidism**	**Total**
20-40	3	4	30	0	37
Row %	8.11%	10.81%	81.08%	0%	100%
Col %	33.33%	14.29%	26.79%	0%	23.87%
40-60	5	17	60	4	86
Row %	5.81%	19.77%	69.77%	4.65%	100%
Col %	55.55%	60.71%	53.57%	66.66%	55.48%
ABOVE 60	1	7	22	2	32
Row %	3.12%	21.88%	68.75%	6.25%	100%
Col %	11.11%	25%	19.64%	33.33%	20.65%
TOTAL	9	28	112	6	155
Row%	5.81%	18.06%	72.26%	3.87%	100%
Col%	100%	100%	100%	100%	100%

Chi square : 4.76, df:6 p: 0.574

Subclinical Hypothyroidism was seen maximally seen (21.88%) in persons of age group above 60 years with mean age of 53. The relation of Subclinical Hypothyroidism with age appeared to be insignificant.

Table 6: Association between thyroid profile and Gender of study subjects

Gender	Hypothyroidism	Subclinical Hypothyroidism	Normal	Hyperthyroidism	Total
Male	4	9	35	4	52
Row%	7.69%	17.31%	67.31%	7.69%	100%
Col%	44.44%	32.14%	31.25%	66.66%	33.55%
Female	5	19	77	2	103
Row%	4.85%	18.45%	74.76%	1.94%	100%
Col%	55.55%	67.86%	68.75%	33.33%	66.45%
Total	9	28	112	6	155
Row%	5.81%	18.06%	72.26%	3.87%	100%
Col%	100%	100%	100%	100%	100%

Chi square:3.72 df:3 p:0.293

Both sexes appear to be equally affected by subcinical hypothyroidism with a small female predominance. The P value indicates that there is not much significance.

Table 7: **Association between thyroid profile and Duration of Diabetes of study subjects**

Duration of Diabetes (In Years)	**Hypothyroidism**	**Subclinical Hypothyroidism**	**Normal**	**Hyperthyroidism**	**Total**
1-5	7	10	62	3	82
Row%	8.54%	12.20%	75.61%	3.66%	100%
Col%	77.77%	3.57%	55.36%	50%	52.90%
6-10	0	8	14	3	25
Row%	0%	32%	56%	12%	100%
Col%	0%	28.57%	12.5%	50%	16.13%
11-15	0	4	15	0	19
Row%	0%	21.05%	78.95%	0%	100%
Col%	0%	14.29%	13.39%	0%	12.26%
16-20	2	1	13	0	16
Row%	0%	6.25%	81.25%	0%	100%
Col%	0%	3.57%	11.61%	0%	10.32%
Above 20	0	5	8	0	13
Row%	0%	38.46%	61.54%	0%	100%
Col%	0%	17.86%	7.14%	0%	8.39%
TOTAL	9	28	112	6	155
Row%	5.81%	18.06%	72.26%	3.87%	100%
Col%	100%	100%	100%	100%	100%

Chi square:21.85 df:12 p:0.03

Subclinical Hypothyroidism affects maximal (38.46%) individuals who have had diabetes for more than 20 years. Mean age is 10.5 years. P value indicates that there is significant association between the duration of diabetes and subclinical hypothyroidism.

DISCUSSION:

Proportion of Subclinical Hypothyroidism:

Out of the 155 individuals included in the study, 112 had normal thyroid function. This accounted for around 72% of the cases. 28 individuals had subclinical hypothyroidism. This accounted for 18%. 9 individuals showed overt hypothyroidism. The study showed significant association of Subclinical Hypothyroidism with Diabetes Mellitus.
A study was conducted in Greece in 2010, where the prevalence of SCHT was 12.4%[19] . In the study in Segovia, Spain, it was 10.7%[20], and in the Fremantle Diabetes Trial, it was 8.8%. Our study had a higher rate of Subclinical Hypothyroidism compared to other studies, this could be because, most of the subjects studied under this study, belonged to the lower socio-economic class. Since they would have little knowledge about the possible complications of their illness and its preventive measures the proportion could be high.

Age Distribution

The individuals included in the study were separated based on groups into ages 20-40 years, 40 – 60 years, and more than 60 years. It was observed that majority of the members included in the study fell into the age groups 40 to 60 years (55.5%). However, even though the overall individuals included in the study was higher in the 40 to 60 years age group, the prevalance of SCHT was higher in the above 60 years group, with 7 individuals in this group having SCHT (21 percent in the age group). However, the stratification of the observed individuals based on age did not prove to be of any statistical significance (p value 0.574). The average age of individuals with DM and a normal thyroid function test was 49.25 years and average age of those who had DM and SCHT was 53.1 years. The age stratification was not significant statistically in the Greece trial as well (p value 0.17)[19]. The average age of diabetic

individuals with an abnormal thyroid function was 65.54 years, compared to 67.12 years in diabetic individuals with a normal thyroid function. There was also no significant difference in age in the Fremantle Diabetes Study as well. One study that showed a statistically significant increase in the prevalance of SCHT in Type 2 DM was by Kim et al, where the mean age of patients with a normal thyroid status was 57.9 years and those with SCHT was 61.8 years[21].

In Karnataka, India, a study in a medical college on hundred and fifteen individuals was performed and the mean age was similar to ours 54.83 years. Another study in South India had a mean age of 58.77 years[23]. These two studies had similar age group stratification which possibly indicates that the prevalance of SCHT in DM in India may occur at a slightly younger age. However more trials are necessary to substantiate this observation.

Gender Distribution:

The participants of the study were divided based on the gender and it was observed that 53 individuals out of 155 were males (33.5 percent), and out of 155 females (66.5 percent). Among the male population, 35 individuals (67 percent males) had normal thyroid function, 9 had SCHT (17 percent) and 4 had overt HT (7.6 percent). Among the females, 77 individuals (74 percent females) had normal thyroid function, 19 had SCHT (18 percent) and 5 had overt HT (5 percent). The prevalance of SCHT in patients with DM is more prominent in females, but this observation has been statistically insignificant in the study ($p = 0.293$).

Most of the trials conducted for similar aims have noticed an asimilar pattern of distribution of patients. The Fremantle Diabetes Study was done exclusively in females and had a lower prevalence of SCHT of about 8.7%[20] compared to 18 percent in our study. Chen HS et al revealed in a study in Taiwan that SCHT was 5.3% in males and 8.4% in females with type 2 DM[24]. In the Greek study, the prevalence was much higher at 18.5% in females, and 5.5 percent in males, the male prevalence being almost comparable to other studies[19].

In the Indian population, only one significant study evaluated the gender distribution of Subclinical Hypothyroidism in type 2 DM, with the proportion being 22 percent in females and 4 percent in males, the female proportion being much higher than in the present study.

CONCLUSION

1. There is a significant proportion of Subclinical Hypothyroidism among individuals having Diabetes Mellitus. Therefore, regular screening for thyroid abnormalities in all diabetic patients will allow early treatment of subclinical thyroid dysfunction.
2. The proportion of Subclinical Hypothyroidism among individuals having Diabetes Mellitus is higher in females than males.
3. There is a significant relationship between proportion of Subclinical Hypothyroidism and the duration of diabetes mellitus.
4. There is no significant relationship between proportion of Subclinical Hypothyroidism in Diabetes and age, H/o Hypertension or tuberculosis.

LIMITATIONS

1. The presence of Anti – TPO antibodies (antibodies to thyroid peroxidase) was not included in the study, which is shown to have significantly higher levels in patients with Subclinical Hypothyroidism in many studies.
2. The presence and absence of diabetic complications in patients with Subclinical Hypothyroidism was not analysed.
3. There was a lack of similar studies performed in India to compare and contrast.

ACKNOWLEDGEMENT

The authors thank the staff members of Biochemistry, Endocrinology and General Medicine MMCRI, Mysore for their support. The Author also Thank the ICMR. The authors are also grateful to authors/editors/ publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

REFERENCES

1. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res. 2007;125: 217-230.

2. Ko SH & Cha BY. Diabetic Peripheral Neuropathy in Type 2 Diabetes Mellitus in Korea. Diabetes Metab J. 2012; 36(1): 6–12.

3.International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Brussels, Belgium: International Diabetes Federation, 2013.

4. Douglas S. Ross subclinical hypothyroidism. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's The Thyroid: A fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 1001-6.

5. Ayala AR, Danese MD, Ladenson PW. When to treat mild hypothyroidism. Endocrinol MetabClin N Am 2000;29:399-415.

6.Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al.The spectrum of thyroid disease in a community. The Wickham, survey.ClinEndocrinol (Oxf) 1977;7:481-93.

7. Sawin CT, Castelli WP Hershman JM, McNamara P Bacharach P 21. , The aging thyroid. Thyroid deficiency in Farmingham study. Arch Intern Med 1985;145:1396-88.

8. Geul KW, van Sluisveld IL, Grobbee DE, Docter R, de Bruyn AM, Hooykaas H, et al. The importance of thyroid microsomal antibodies in development of elevated serum TSH in middle age women; Association with serum lipids.ClinEndocrinol (Oxf) 1993;39:275-80.

9. Vanderpump MP Tunbridge WM, French JM, Appleton D, Bates D, ,Clark F, et al. The incidence of thyroid disorders in community.A 20 year follow up of the Wickham survey. ClinEndocrinol 1995;43:55-68.

10. Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P Maccherini D, Leoli F, et al. The spectrum of thyroid disorders in iodine deficient community: The Pescopagano Survey. J ClinEndocrinolMetab 1999;84:561-6.

11. Kung AW, Janus ED. Thyroid dysfunction in ambulatory elderly Chinese subjects in an area of borderline iodine intake. Thyroid 1996;6:111-4.

12.Duntas LH, Orgiazzi J, Brabant G. The Interface between thyroid and diabetes mellitus.ClinEndocrinol (Oxf). 2011;

13.Kasper, Braunwald, Fauci et al; Subclinical hypothyroidism. Harr ison's principles of internal medicine, 16 th Edition, 2004;Vol 2, 2110 – 11.

14. Unsal C, Oran M, Tureli HO, et al. Detection of subclinical atherosclerosis and diastolic dysfunction in patients with schizophrenia. Neuropsychiatr Dis Treat. 2013;9:1531-7.

15. Mansourian, A.R., A review on cardiovascular diseases originated from subclinical hypothyroidism.. Pak. J. Biol. Sci., 2012;15: 58-67.

16. Kahaly, George J. "Cardiovascular and atherogenic aspects of subclinical hypothyroidism." Thyroid 10.8 (2000): 665-679.

17. Schlienger JL, Anceau A, Ghabrier G, North ML,Stephan F. Effect of diabetic control on the level of circulating thyroid hormones.Diabetologia 1982; 22: 486-8.

18. K.SatyaNarayana, "Evaluation of Thyroid Profile Among The Diabetic Patients in South Indian Rural Population" Indian J EndocrMetab [serial online] 2012 [cited 2014 Jan 24];16:514-24

19. Diez JJ, Sanchez P, Iglesias P. Prevalence of thyroid dysfunction in patients with type 2 diabetes. ExpClinEndocrinolDiabetes. 2011;119(4):201-7

20. Chubb SA, Dawis WA, Inman Z. Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: The Fremantle Diabetes Study.ClinEndocrinol (Oxf) 2005;62:480-6.

21.Papazafiropoulou A, Sotiropoulos A, Kokolaki A, Kardara M, Stamataki P, Pappas S. Prevalence of Thyroid Dysfunction Among Greek Thype 2 Diabetic Patients Attending an Outpatient Clinic. J Clin Med Res. 2010;2(2):75-78

22. Kim BY, Kim CH, Jung CH, Mok JO, Suh KI, Kang SK. Association between subclinical Hypothyroidism and severe diabetic retinopathy in Korean patients with Type 2 diabetes.Endocr J. 2011 Sep 17. [Epub ahead of print].

23. Swamy RM, Naveen K, Srinivasa K, Manjunath GN, Prasad BDS, Venkatesh G. Evaluation of Hypothyroidism as a complication in Type 2 Diabetes Mellitus. Biomedical Research 2012;23(2):170-172.

24. Chen HS, Wu TE, Jap TS. Subclinical Hypothyroidism is a risk factor for nephropathy and

cardiovascular diseases in type 2 Diabetic patients. Diabet Med 2007;24:1336-44.