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A Pilot Observational Study to Assess Euthyroid Sick Syndrome Among Type 2 Diabetes Mellitus Patients

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ABSTRACT

Introduction: "Thyroid diabetes" merely describes the association of altered thyroid hormones synthesis in worsening the glycemic control. Great reduction in extrathyroidal triiodothyronine (free/Total) formation occurs in nonthyroidal illnesses like diabetes.
Aim & Objectives: An observational study was designed to assess and observe serum free T3 (fT3), free T4 (fT4) and TSH to evaluate euthyroid sick syndrome and to find out: 1. if there was any correlation of fT3 with duration of diabetes, 2. Its association with non-thyroidal illness.
Materials and Methods: The present observational study was conducted in the department of Biochemistry in collaboration with Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana-Ambala, Haryana, India. 100 clinically diagnosed type 2 diabetic mellitus patients in the age group of 35-70 years were selected by simple random method. Glycated hemoglobin (HbA1c) was measured by Ion Exchange Resin method to confirm type 2 diabetes mellitus and serum fT3, fT4 and TSH were measured by Microplate Chemiluminescence Immunoassay (CLIA) method to assess thyroid disorders. The obtained data were analysed using SPSS (Statistical Package for the Social Sciences) version 23.
Results: Occurrence of thyroid disorders among T2DM patients was found to be 62%, of which 33% exhibited as low fT3 state, 28% as hypothyroidism (32.2% primary hypothyroidism and 67.8% subclinical hypothyroidism) and 1% as clinical hyperthyroidism. Duration of type 2 diabetes was statistically correlated showing negative relation with serum fT3 level.
Conclusion: The present study outlines the higher occurrence of thyroid disorders among people suffering from T2DM. Low fT3 state and hypothyroidism are more obviously seen in T2DM patients, and incidence increases with duration of T2DM

Key Words: Thyroid diabetes, Low fT3 state, Hypothyroidism, Type 2 diabetes mellitus, Euthyroid sick syndrome,

INTRODUCTION

Diabetes mellitus (DM) is the most frequent metabolic disorder which shares the feature of increased blood glucose, including decreased glucose utilization, and increased glucose production because of complete dearth of insulin hormone or insulin resistance. (1) The figure of persons inhabiting with this disorder is anticipated to go up from 366 million in 2011 to 552 million by 2030, if no critical act is undertaken. (2) It is estimated that India constitutes about 50.8 million individuals with DM and the figure is projected to rise to 70 million by 2025. (3) Endocrine dysfunctions are growing all over the world. Globally, thyroid disorders stand as second ranking among hormonal disorder after DM. (4)

The term "thyroid diabetes" reflects the impact of alterations of thyroid hormones in the worsening of glycemic control. (5) The association between the two endocrine disorders had come in light since 1979 after the study conducted by Hecht et al who emphasized on the significance of clinical examination of diabetic persons to get knowledge of thyroid disease. (6,7). DM comes into view to govern thyroid functioning in 2 points; initially at the point of hypothalamic modulation of thyroid stimulating hormone (TSH) secretion and secondarily at the formation of T3 from T4 in the tissues. Pronounced hyperglycemia triggers reversible decline of the action as well as the level of hepatocyte T4-5-deiodinase. The hallmark of thyroid derangement includes a state of "Low T3 syndrome" which is presented as diminished level of triiodothyronine (total and unbound), increased concentrations of reverse triiodothyronine and almost baseline level of thyroxine and TSH among poorly managed diabetics. Researches point out that the prolonged period of glycemic management governs the serum triiodothyronine concentrations. (8,9). Approximately 80% of T3 is formed by extrathyroidal T4 deiodination to T3 and about 20% by thyroid tissue. Almost 50% or more reduction in T3 levels occurs in patients with various acute and chronic nonthyroidal infirmities such as acute infections, myocardial infarction, acute starvation and chronic malnutrition, diabetes mellitus, hepatic, pulmonary and renal diseases. These illnesses cause reduced pituitary capacity to react to reduced concentration of THs. (10) In diabetes, lowered production of T3 might be associated with weakened glucose utilization and insulin treatment inversed the effect. (11) As it is evident that poorly managed diabetic patients will have low thyroid hormones secretions, especially T3, so, the present study was designed to assess serum free T3 (fT3), free T4 (fT4) and TSH to evaluate euthyroid sick syndrome i.e., "low fT3 state" and to find out the correlation of fT3 with duration of diabetes, if any among type 2 diabetic patients.

MATERIALS & METHODS

The present observational study was hospital-based; conducted for two years (2015-2017) by selecting 100 clinically diagnosed type 2 diabetic mellitus patients.

The study was conducted in the department of Biochemistry in collaboration with Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana-Ambala, Haryana, India. The subjects were selected in the age range of 35-70 by simple random sampling method. The study was being approved by Institutional Ethics Committee vide letter no. 449 dated 08.04.2015. All the subjects (age & sex matched) were enrolled on the basis of inclusion and exclusion criteria. Demographic information of patients like age and sex were taken and detailed data related to present and past history, any illness and medication were completed as per the designed proforma.

Glycated hemoglobin (HbA1c) was measured by Ion Exchange Resin method to confirm type 2 diabetes mellitus and serum fT3, fT4 and TSH were measured by Microplate Chemiluminescence Immunoassay (CLIA) method to assess thyroid disorders. (12-15) The obtained data were analysed using SPSS (Statistical Package for the Social Sciences) version 23. Student's t-test was employed and Pearson correlation was achieved for the correlation of bivariate analysis. Demographic data were presented by using Excel sheet.

RESULT

The baseline characteristics in the present study were 50 male T2DM cases had mean age as 57.40 ± 5.93 years and 50 female T2DM cases had mean age as 55.96 ± 7.39 years. The mean HbA1c value among T2DM male cases was found to be 8.53 ± 2.02% and that of T2DM female cases was found to be 8.66 ± 1.90%. Out of 100 diagnosed cases of T2DM, 63 cases were poorly controlled (HbA1c ≥ 7.5%) and 37 cases were categorised under good glycemic status (HbA1c < 7.5%). The mean duration of diabetes (In years) among type 2 diabetic male patients was found to be 5.48 ± 5.99 and that of type 2 diabetic female patients was found to be 5.20 ± 5.42.

In the present study, there were more T2DM patients having low serum fT3 levels i.e., 61 out of 100. The occurrence of diseases of thyroid among T2DM patients was found to be 62%, of which 33% exhibited as low fT3 state, 28% as hypothyroidism (32.2% primary hypothyroidism and 67.8% subclinical hypothyroidism) and 1% as clinical hyperthyroidism. (Figure 1)

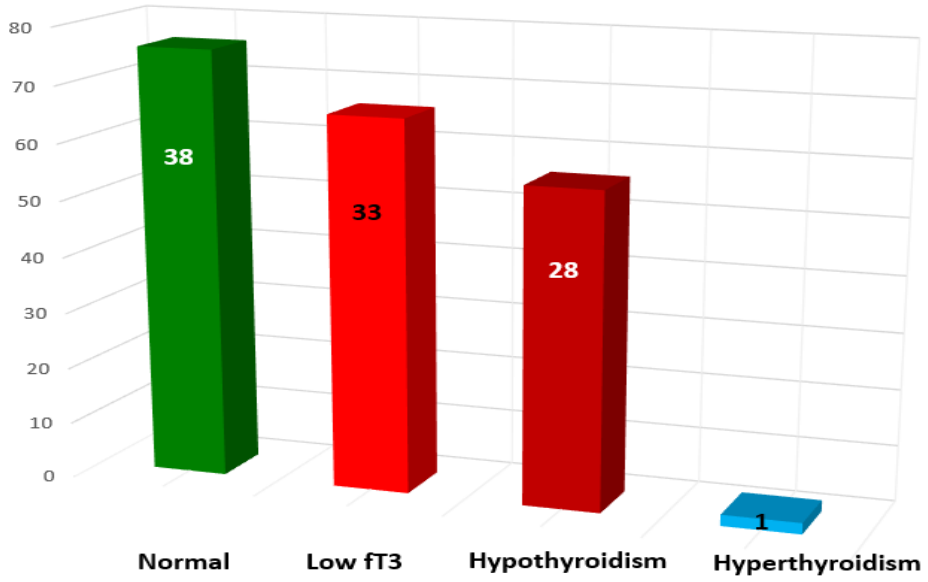

Figure 1: Diagram showing occurrence of thyroid disorders among T2DM patients.

In the present study, serum TSH level were negatively correlated with serum fT3 & fT4 levels which was statistically significant (Pearson correlation value for fT3 was -0.254, p value = 0.11 and for fT4 was -0.340, p value = 0.001). Also, duration of diabetes among T2DM cases was negatively correlated with serum fT3 level and the correlation was found to be significant statistically. (Table 1)

Table 1: Correlation of diabetic duration with serum fT3, fT4 and TSH level among T2DM cases.

PARAMETER		fT3	fT4	TSH
DURATION	Pearson Correlation	-0.220*	-0.144	-0.006
	P value	0.028	0.154	0.950

Two-tailed Pearson correlation

In the present study, there were 80 T2DM patients categorised under having diabetic duration < 10 years whereas, there were 20 T2DM patients categorised under having diabetic duration ≥ 10 years. The numerical representation of 100 T2DM patients suffering from thyroid disorders is depicted in the table 2.

Table 2: Distribution of 100 T2DM patients suffering from thyroid disorders on the basis of diabetic duration

Duration of Diabetes	Number of T2DM patients			
	Normal Thyroid Function	Euthyroid Sick syndrome (low fT3 state)	Hypothyroidism	Hyperthyroidism
< 10 years (N = 80)	33	23	23	01
≥ 10 years (N = 20)	05	05	10	Nil

DISCUSSION

T2DM is worldwide growing burden which may be associated with the thyroid disorders in later life in general population. (16) Diabetes mellitus and thyroid disorders equally impact on each other. (17) Diabetes mellitus cause abnormalities in various tests carried out for thyroid functioning: including decreased plasma total and unbound T3 levels, raised reverse T3 concentrations and normal or enhanced plasma TSH level. (18)

In a study done by Panneerselvam et al., it was revealed that serum total and free thyroid hormone levels were considerably lesser in diabetic cases in contrast to individuals without having diabetes and serum TSH level was observed to be considerably high in such patients in contrast to normal individuals. (19). Another study done by Islam et al. also furnished the data in which there was significantly lower levels of fT3 in T2DM patients in contrast to people without having diabetes, while concentrations of serum fT4 and TSH were not significant among T2DM patients as compared to normal individuals. (20)

The thyroid hormones (THs) are insulin adversary and affect the physiological function of insulin hormone in some way that could impose low levels of THs in T2DM. (19) Insulin is an anabolic hormone that will increase the fT4 level and depress the fT3 level through the inhibition of hepatocyte change of T4 to T3. This may explain low fT3 state in T2DM. DM affects thyroid functioning at 2 sites: first, at the stage of hypothalamic command of TSH secretion and second, at the point of translation of T4 to T3 in the peripheral tissues. (21)

The findings shown in figure 1 were higher in present study in comparison to previous studies. In a study done by Suhail, it was revealed that thyroid disorders among 30 type 2 diabetic patients existed as 20% and the trend of thyroid disorders was as 6.6% as low T3 state, 10% as hypothyroidism (33.3% as clinical hypothyroidism and 66.6% subclinical hypothyroidism) and 3.3% as clinical hyperthyroidism. (22) Further, it stated that hypothyroidism was more common thyroid disorder and this statement was in agreement with the research carried out by perros et al, stating that increased proportions of subclinical hypothyroidism found among all prototypes of thyroid disorder. (23) Additionally, in a study done by AL-Wazzan et al, euthyroid sick syndrome (characterized by low T3 state) comprised of 15.7% among the patients of T2DM. (24) In another study, it was revealed that thyroid disorder was found as 20% among 100 DM type 2 patients. In this study, low fT3 state (euthyroid sick syndrome) was found as 7%, 10% had hypothyroidism (40% primary hypothyroidism and 60% subclinical hypothyroidism) and 3% had hyperthyroidism. (25) So, it can be interpreted that low T3 state and subclinical hypothyroidism are commonest thyroid disorder among patients of T2DM in the present study. The biochemical mechanism for this abnormality is due to the fact that

hyperglycemia may possibly alter the post-translational glycosylation of hypothalamic TRH, thereby affecting the biological activity. (26)

In research done by Tirkey et al, it was concluded that the incidence of thyroid dysfunction increased with duration of diabetes which was clinically and statistically significant. (27) Alteration in thyroid hormones occurred either during early or later period of diabetic pathogenesis and led to thyroid disorder among T2DM patients. In a study done by Chandel et al., it was stated that the hypothyroidism was found in T2DM with duration of diabetes less than ten years, as well as greater than ten years of diabetic duration, the prevalence being 35.87% & 22.5% respectively. (28) However, a study done by Diez et al. did not observe any significant association of the existence of thyroid disorder with diabetic duration among T2DM and mentioned that thyroid dysfunction occurred at any point of diabetes. (29) In research done by Ravishakar et al., it was revealed that though the proportions of thyroid disorder were high among T2DM cases having diabetic interval less than ten years (61.1%) in contrast to those having diabetic interval greater than ten years (10%), increase of thyroid disorder did not depend on increased duration of diabetes. (30) In a study done by Ogbonna et al, it was revealed that DM duration >5 years was a risk factor for thyroid dysfunction and increasing duration of DM may be a risk factor in the prevalence of thyroid dysfunction as chronic hyperglycaemia impairs the peripheral deiodination of T4 to T3 leading to thyroid dysfunction. (31)

CONCLUSION AND FUTURE PERSPECTIVES

The present study outlines the higher occurrence of thyroid disorders among people suffering from T2DM. Low fT3 state and hypothyroidism are obviously seen in T2DM patients. The simultaneous existence of both hormonal conditions impacts clinical scenario and laboratory outcomes directing screening, diagnostic and therapeutic approaches. If recognition of altered thyroid hormone parameters among diabetic individuals at any stage is not achieved, it may often be a prime reason of poor supervision of the subjects. Thus, regular screening of thyroid hormones, especially once or twice a year TSH measurement and thyroid autoantibody is strongly recommended in all individuals with more focus on diabetic population to identify and manage the complications in order to reduce all cause of morbidity and mortality, thus providing better health care and longevity to the persons.

However, the present study is limited to small diabetic people attending hospital, Further research design is needed to focus on large population-based longitudinal study to validate the association of thyroid hormones in clinical settings. Additional laboratory data like blood pressure, lipid profile and biochemical parameters reflecting diabetic complications should be included to recognize entirely the role of thyroid disorders in type 2 diabetic patients and the risks concerned.

Declaration by Authors

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