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STUDY OF THYROID FUNCTIONS IN TYPE 2 DIABETES MELLITUS AND RELATIONSHIP WITH OBESITY IN A TERTIARY CARE HOSPITAL, BANKURA, WEST BENGAL

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ABSTRACT

Type 2 diabetes mellitus (T2 DM) is a well-recognized cause of premature death, disability and multi-organ disturbances and the rising trend of it invite more metabolic problems worldwide. Central obesity along with sedentary life style is one of the components of syndrome-X and a major risk factor of T2 DM. The objective of the study was to find out the inter-relationships among thyroid function (Serum TSH, T4, T3 levels); glycemic status (HbA_{1c} and fasting plasma glucose, FPG) and obesity in patients of T2 DM. A descriptive and cross-sectional study was conducted over a Period of 12 months among 87 patients suffering from T2 DM (uncontrolled) without known thyroid or kidney disease, and attending the Diabetes and Endocrinology Special Clinic of BSMCH, Bankura. The selected patients were interviewed and clinically examined to get the vital and physical statistics. Blood samples were collected and biochemical analyses were done following standard protocols. Data obtained were codified and analysed using appropriate

statistical methods and software package. This study shows that duration of diabetes was significantly related to TSH and BMI. HbA_{1c} had significant positive relationship with TSH, BMI and negative relationship with T4, T3. FPG had significant negative relation with T4. BMI was significantly related to TSH, T4, T3. Metabolic disturbances in diabetes can be manifested as hypothyroidism and obesity and these problems are increased with the chronicity and uncontrolled glycemic conditions.

KEYWORDS: Diabetes mellitus; Subclinical hypothyroidism; HbA_{1c}; BMI.

INTRODUCTION

Diabetes mellitus (DM) is one of the most commonly encountered non-communicable diseases (NCDs) in the developed as well as in the developing countries, can affect almost all the organs in the body and is a well-recognized cause of premature death and disability; increasing the risk of multi-organ dysfunction like cardiovascular diseases, kidney failure, blindness, neuropathy and peripheral vascular diseases.[1] It is a serious, chronic endocrine disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces.[2]

It was seen that global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in adults.[3] This may be due to an increase in associated risk factors such as being overweight or obese.[2,4] Worldwide data suggests that more than 90% of diabetic cases belong to type 2 diabetes mellitus (T2DM).[4]

Uncontrolled hyperglycemia for prolonged duration leads to metabolic, endocrinal, micro and macrovascular as well as systemic complications. DM and thyroid diseases are most common endocrine disorders occurring concurrently in adults as thyroid hormones are insulin antagonist.[4] The diagnosis of thyroid dysfunction in diabetic patients based on clinical examination is difficult, because poor glycemic control resembles some hyperthyroid features, such as weight loss despite increased appetite, fatigue and on the other hand diabetic nephropathy is mistaken for hypothyroidism because it manifests as weight gain, edema, fatigue and pallor.[2]

It was observed in many researches that the prevalence thyroid dysfunction was much higher in diabetic patients.[5,6] In Japanese population subclinical hypothyroidism (SCH) among T2DM was 8.7%.[7] A very high incidence (29%) of thyroid dysfunction among diabetic

patients in Punjabi population was also noted.[8] Available literatures revealed that the prevalence of thyroid dysfunction in T2DM was 28.33%.[9] So a study was conducted to assess the thyroid functions (TSH, T4, T3) in type 2 diabetic patients to find out the relationship between thyroid functions, body mass index and glycemic status of the patients.

MATERIALS AND METHODS

Eighty seven participants were chosen from the patients attending the Diabetes and Endocrinology Special Clinic of Bankura Sammilani Medical College and Hospital (BSMCH) by systematic random sampling method and the tertiary care institution based descriptive cross-sectional study was conducted over a period of 1 year (August, 2016 to July 2017) after getting the ethical clearance from Institutional Ethics committee of BSMCH according to the following inclusion and exclusion criteria.

Inclusion criteria: Diagnosed T2DM patients who gave consent spontaneously to be the participants of the research work and whose BP found to be < 130 / 80 mm Hg with or without medication were included. As it was a cross-sectional study, repeat examination of same persons were avoided.

Exclusion criteria

- Moribund and critically ill patients or who were critically ill within last 3 months.
- Known case of type 1 or any other types of diabetes mellitus.
- Patients who were reluctant to take part in the study.
- Patient who was on medications for thyroid disorder or any other endocrinopathy or taking steroids or any medications that might influence thyroid function (eg. lithium, dopamine, glucocorticoids etc.)
- Patient who was suffering from chronic liver disease.
- Patient who was suffering from any kind of known malignancy or receiving any anticancer drug.
- Patient who had been undergone thyroid surgery, pancreatic surgery, pituitary surgery.
- Pregnancy with diabetes mellitus and gestational diabetes mellitus.
- Patients of age > 70 years or < 20 years.

Participants were interviewed with a predesigned, pretested questionnaire and after taking consent from them blood sample of 5 mL was drawn as per standard protocol of phlebotomy and kept in proper vials. Serum was separated from plain vial by centrifugation. Enzyme-

Linked Immunosorbent assay was done for assessment of TSH, T4 and T3, fasting plasma glucose (FPG) was estimated by Glucose oxidase- peroxidise method and HbA_{1c} was estimated by immunoturbidimetric method.

BMI was calculated by the following formula

$$BMI = \frac{\text{Weight (in kg)}}{\text{Height}^2 \text{ (in m)}}$$

RESULT AND DISCUSSION

Out of 87 participants, female participants outnumbered the male participants. The ratio of Male: Female = 40: 47 = 1: 1.175. Among all participants, 44.8% belonged to 20- 40 years, 50.6% in 40- 60 years and rest 4.6% belonged to more than 60 years of age.

Table. 1: Descriptive statistics of various attributes of the participants.

Attributes	Mean	Range	SD	Median	SE of mean
Age (years)	43.110	21- 67	9.476	41	1.016
BMI (kg/ m^2)	27.737	19.83- 34.12	2.756	27.940	0.296
Duration of DM (years)	2.980	< 1- 10	2.151	3.000	0.231
HbA_{1c} (%)	8.125	6.36- 10.69	1.018	8.020	0.109
FPG (mg/ dL)	147.804	95.10- 220.10	28.494	148.600	3.055
TSH (mIU/ L)	3.338	0.88- 10.36	2.167	2.650	0.232
T4 (µg/ dL)	7.692	5.61- 10.60	1.154	7.450	0.124
T3 (ng/ mL)	0.674	0.28- 1.11	0.191	0.650	0.020

Low T3 (< 0.5 ng/mL) was found in 17.2% of all T2DM patients; out of which 33.3% were female and 66.7% were male participants.

Table. 2: Comparison of different attributes as per gender.

Attributes	**Male (Mean ± SD)**	**Female (Mean ± SD)**	**Independent 't' / Mann-Whitney* 'U'; df**	**p value (2- tailed)**
Age in (years)	46.08 ± 10.38	40.60 ± 7.90	t = 2.792; 85	**0.006**
Duration of DM (years)*	4.95 ± 5.01	4.45 ± 4.46	U (Z) = 885.5; 0.47	0.639
BMI (kg/m^2)	26.60 ± 2.67	28.70 ± 2.47	t = -3.803, 85	**< 0.001**

(p value < 0.05 was taken as statistically significant and < 0.01 as highly significant result)

The males were found to be higher in age and had longer duration of suffering from diabetes mellitus. BMI were found significantly more in females than males.

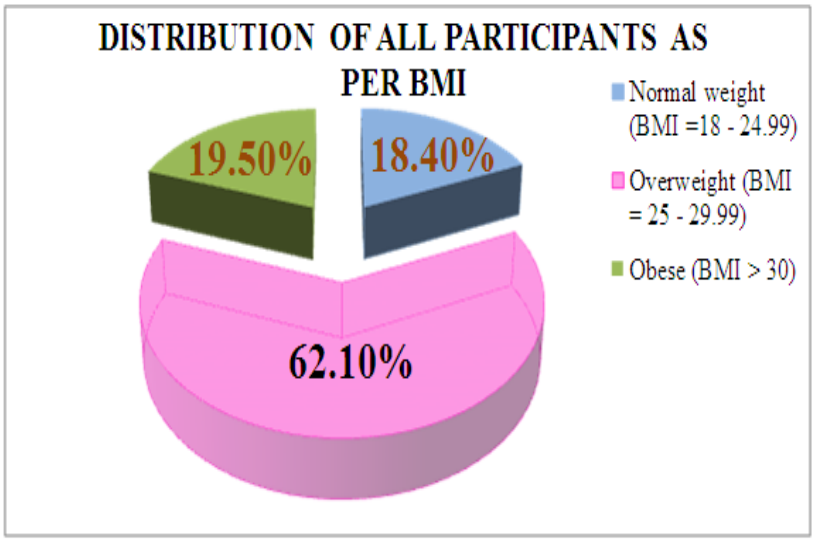

Figure. 1: Distribution of participants according to BMI.

Table. 3: Comparison between BMI groups and HbA_{1c} groups.

BMI groups (kg/ m^2)		HbA_{1c} (%)	
		< 7	≥ 7
18- 24.99	Number	9	7
	% within BMI group	56.2	43.8
25- 29.99	Number	6	48
	% within BMI group	11.1	88.9
≥ 30	Number	0.0	17
	% within BMI group	0.0	100.0

Here, Pearson's Chi-Square significance < 0.001. Hence, BMI groups and HbA_{1c} groups were related with high significance. Increased BMI induced uncontrolled glycemic status.

Table. 4: Comparison between BMI groups and TSH groups.

BMI group (kg/m^2)		TSH group (mIU/ L)		
		< 5.5	5.5- 10	≥ 10
18- 24.99	Number	14	2	0
	% within BMI group	87.5	12.5	0.0
25- 29.99	Number	39	14	1
	% within BMI group	72.2	25.9	1.9
≥ 30	Number	14	3	0
	% within BMI group	82.4	17.6	0.0

Here, Pearson's Chi-Square significance= 0.689; hence, no significant correlation was obtained in between BMI groups and TSH groups. Medicine like metformin and life-style modifications reduces body weight but has no effect on TSH. Hence, higher TSH values may be obtained in the diabetic population with normal or overweight persons on therapy for prolonged duration.

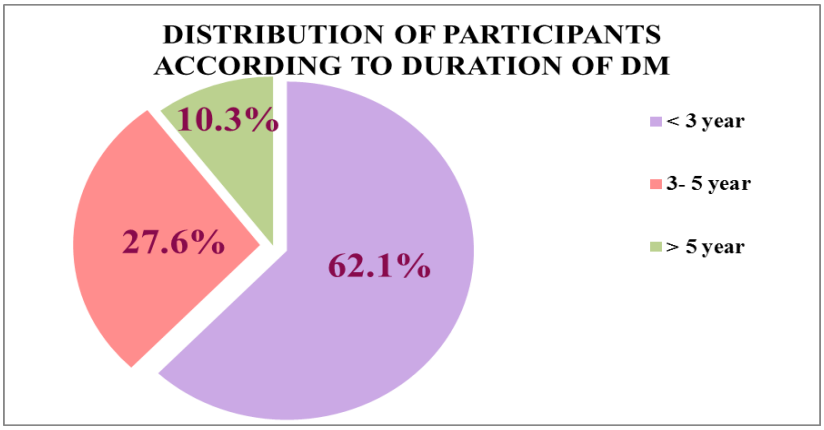

Figure. 2: Distribution of participants according to chronicity of diabetes mellitus.

Most of the participants (80.5%) were suffering from uncontrolled T2DM (FPG ≥ 126 mg/ dL).

All the participants had T4 within the reference range. Subclinical hypothyroidism was found in 21.84% among all T2DM patients; among whom female were 57.89% and male 42.11%.

Table. 5: Comparison of TSH groups in accordance with Duration of DM.

TSH groups (mIU/L)		Duration of DM (in years)		
		< 3	3- 5	> 5
< 5.5	Count frequency	51	12	4
	% in TSH Group	76.1%	17.9%	6.0%
5.5- 10	Count frequency	3	12	4
	% in TSH Group	15.8%	63.2%	21.1%
≥ 10	Count frequency	0	0	1
	% in TSH Group	0.0%	0.0%	100.0%
Total	Count frequency	54	24	9
	% in TSH Group	62.1%	27.6%	10.3%

It was obvious from Table- 5, the participants were prone to develop hypothyroidism with the advancement of chronicity of diabetes mellitus.

It was noted from Table- 6, that age showed statistically highly significant positive correlation with duration of disease ($r = 0.387$; $p < 0.001$) and significant negative correlation with FPG concentration ($r = -0.231$; $p < 0.032$). It was also found that the body weight had a linear positive highly significant correlation with serum markers of diabetes i.e. fasting plasma glucose ($r = 0.547$; $p < 0.001$) as well as HbA_{1c} ($r = 0.702$; $p < 0.001$) meaning that obese / overweight people might have less control over their glycemic status. It was very much obvious that serum T3 and T4 were related significantly and positively among themselves. TSH had highly significant positive correlation with age and duration of diabetes mellitus but significant negative correlation with T3 and T4 (<0.001).

Table. 6: Correlation table showing the strength of association between parameters.

		Age	Duration of DM	BMI	HbA_{1c} (%)	FPG (mg/ dL)	TSH (mIU/ mL)	T4	T3
Age	Pearson Correlation	1	0.396	0.014	-0.053	-0.231	0.289	-0.187	-0.198
	Significance (2-tailed)		**<0.001**	0.899	0.624	**0.032**	**0.007**	0.083	0.066
Duration of DM	Pearson Correlation	0.396	1	0.045	0.002	-0.072	0.639	-0.335	-0.354
	Significance (2-tailed)	**<0.001**		0.680	0.986	0.506	**<0.001**	**0.001**	**0.001**
BMI	Pearson Correlation	0.014	0.045	1	0.702	0.547	-0.004	0.155	-0.003
	Significance (2-tailed)	0.899	0.680		**<0.001**	**<0.001**	0.974	0.152	0.981
HbA_{1c}	Pearson Correlation	-0.053	0.002	0.702	1	0.820	-0.009	0.127	0.037
	Significance (2-tailed)	0.624	0.986	**<0.001**		**<0.001**	0.934	0.242	0.733
FPG	Pearson Correlation	-0.231	-0.072	0.547	0.820	1	-0.024	0.087	-0.048
	Significance (2-tailed)	**0.032**	0.506	**<0.001**	**<0.001**		0.822	0.424	0.658
TSH	Pearson Correlation	0.289	0.639	-0.004	-0.009	-0.024	1	-0.628	-0.434
	Significance (2-tailed)	**0.007**	**<0.001**	0.974	0.934	0.822		**<0.001**	**<0.001**
T4	Pearson Correlation	-0.187	-0.335	0.155	0.127	0.087	-0.628	1	0.537
	Significance (2-tailed)	0.083	**0.001**	0.152	0.242	0.424	**<0.001**		**<0.001**
T3	Pearson Correlation	-0.198	-0.354	-0.003	0.037	-0.048	-0.434	0.537	1
	Significance (2-tailed)	0.066	**0.001**	0.981	0.733	0.658	**<0.001**	**<0.001**	

N.B. Significant Correlations are given in bold words.

Hyperglycemia is the hallmark of diabetes mellitus and HbA_{1c} is the important diagnostic as well as prognostic parameter of DM, by which we can know the glycemic condition of patient over a period of about 2 months. Obesity is one of the major factors in the pathogenesis of DM and has a central role to produce different types of complications. Obesity or overweight can be measured by the help of body mass index (BMI) which is related to chronicity of the disease as well as glycemic status of the disease.

Obesity is said to be related directly with insulin resistance and thus T2DM and most of the complications are also strongly related to increase BMI. In present study, overweight (62.1%) was predominantly found in the study population followed by obesity of 19.5%, amounting to mean BMI of 27.73 ± 2.75 (SD). Increased value of BMI was readily found in the participants with thyroid dysfunction in respect to euthyroid participants and this was again supported by many previous studies.[6,7,10] In contrary, BMI was found to be reduced in SCH in a Korean study by Kim et al.[11] In the present study BMI was found to be in linear positive highly significant correlation with serum markers of diabetes i.e., fasting plasma glucose and BMI groups were significantly related to the HbA_{1c} groups. These meant that obese / overweight people might have less control over their glycemic status. Rising trend of obesity due to sedentary life style is one of the culprits of developing type 2 diabetes mellitus and metabolic syndrome.[1]

HbA_{1c} in present study was (8.125 ± 1.02) % (Mean ± SD) and the mean was found to be increased in subclinical hypothyroid group. This result were corroborative with the study by Chen et al.[10] [(7.8 ± 1.7) in euthyroid vs. (7.9 ± 2.1) in SCH] but not supported by Kim et al. in his study.[11] Bazrafshan et al. showed mean concentration of HbA_{1c} was found significantly higher in the hypothyroid patients in respect to euthyroid persons and HbA_{1c} was positively correlated with TSH and this result was corroborative with different previous studies.[6] Prevalence of thyroid disorders was more in patients with $HbA_{1c} \geq 7\%$, i.e., in patients having uncontrolled T2DM; this result was in concordance with the study by Khurana et al.[12]

In the present study, mean value of TSH was found to be 3.34 with the SD of 2.167 mIU/ L. Subclinical hypothyroidism was found to be 21.84%, whereas overt hypothyroidism was 1.15%; which was corroborative with the findings in different studies done by different researchers such as Bazrafshan et al.[6] (overall prevalence of SCH 13% and clinical

hypothyroidism was 4%), Singh et al.[8] (overall prevalence of thyroid disorders was 33% out of which primary and subclinical hypothyroidism was 14% and 10%, respectively), Nobre et al.[13] (overall prevalence of thyroid disorders was 12.7% out of which hypothyroidism was 10.7% and 68.7% of hypothyroid patients belonged to SCH), Papazafiropoulouet al.[14] (overall prevalence of thyroid disorders was 12.3%), Demitrost et al.[15] (overall prevalence of thyroid disorders was 31.2% out of which hypothyroidism was 27.7%). Anveetha et al.[16] (overall prevalence of thyroid disorders was 26.7% out of which hypothyroidism was 16.7%), Radaideh et al.[17] (overall prevalence of thyroid disorders was 12.5% out of which SCH was predominant 4.1%), Perros et al.[18] (overall prevalence of thyroid disorders was 13.4% out of which hypothyroidism was 0.9% and SCH 4.8%), Pasupathi et al.[19] (overall prevalence of thyroid disorders was 45% out of which hypothyroidism was 28%), Udiong et al.[20] (overall prevalence of thyroid disorders was 46.5% out of which hypothyroidism was 26.6%), Vikhe et al.[21] (overall prevalence of thyroid disorders was 30% out of which hypothyroidism was 22%) and many more. On the contrary to the present study, Sahu et al.[9] showed in her research that out of all thyroid disorders (28.33%), overt hypothyroidism (15%) was prevalent than SCH (8.33%). In general population without hyperglycaemic conditions SCH (5.5 < TSH value < 10 mIU/ L; adopted from American thyroid Association[22]) accounts for only 3- 8% of the general population.[23] In the present study, SCH was found to be clearly in excess in case of T2DM. It was evident from the present study that females were more prone to suffer from thyroid dysfunction in T2DM than males and this was also supported by different studies.[14,18,21,24] High prevalence of SCH in type 2 diabetic women was also found in the study conducted by Hollowell et al.[25] Since SCH is a well-known risk factor for overt hypothyroidism[7], measures to be taken early to circumvent the problem especially when it is associated with diabetes mellitus.

In DM, due to alterations in the hypothalamo-pituitary-thyroid axis (HPT axis), there is a reduction in the hypothalamic and plasma TRH, pituitary and plasma TSH and TSH secretion rate. Therefore, despite normal peripheral TSH metabolism, response of TSH to TRH is also decreased. Iodide uptake by thyroid gland and peripheral conversion of T4 to T3 are diminished. There are also important structural changes in both thyroid and pituitary glands, accompanied by marked alterations in their secretory activities. In addition to these, deiodination of T4 to T3 is decreased.[16,19] Thus T3 may be lower than the normal in DM. In present study, low T3 values was found in 17.2% of all T2DM patients; out of which 33.3% were female and 66.7% were male participants. It was found that the diabetics also might

have proneness to altered thyroid function. Increased duration of diabetes was found to have a highly significant negative linear correlation with the serum T3 and T4. Duration of DM also had highly significant correlation with TSH. Different studies revealed that the levels of serum T3, T4 were significantly lower in diabetics while serum TSH was significantly higher in diabetics.[8,16,21] Suzuki et al. attributed the abnormal thyroid hormone levels found in diabetes due to the presence of thyroid hormone binding inhibitor (THBI) which hampers peripheral conversion of T4 to T3 by inhibiting the conversion enzyme 5'- deiodinase and possibly produce dysfunction of the HPT axis.[26]

CONCLUSION

It was concluded in the present study that hypothyroidism (mostly in subclinical stage) was found to be an endocrinal complication in cases of long-standing uncontrolled diabetes mellitus and was more prevalent in female patients. SCH were noted to have an increased age, increases chronicity of DM, increased BMI and more uncontrolled glycemic conditions with respect to euthyroid groups. Stringent control of glycemic condition and weight management was found to be the important preventive measures to delay the development and progression of complications.

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