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Alteration of Thyroid Hormone Pictures in Absence of Clinically Evident Thyroid Diseases among Type 2 Diabetic Subjects in a Bangladeshi Population

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Abstract

Background: Thyroid diseases and diabetes mellitus are common endocrine disorders and Euthyroid Sick Syndrome is very common in uncontrolled type2 Diabetes Mellitus.Objective: To evaluate the thyroid hormone pictures in absence of clinical thyroid diseases among type2 diabetic subjects in a Bangladeshi population.

Index terms— euthyroid sick syndrome (ESS), diabetes mellitus, body mass index (BMI).

1 Introduction

iabetes mellitus (DM) is one of the important health problems affecting the major population worldwide. Diabetes mellitus is an endocrine disorder which involves multiple organ systems and leads to significant morbidity and mortality due to accompanying complications. **??**. Diabetes mellitus is characterized by absolute or relative deficiency in insulin secretion or insulin action or both, associated with hyperglycemia and disturbances in carbohydrate, lipid and protein metabolism. 2 Thyroid diseases and diabetes mellitus are the two most common endocrine disorders 3 . Diabetic patients have increased prevalence of thyroid disorder, with hypothyroidism being the most common. 4 In diabetic patients, thyroid dysfunction varies from 2.2% -17%.

Diabetic women are more commonly affected than men. 5 Hypothyroidism is a clinical syndrome occurs from a deficiency of thyroid hormones. It is very common thyroid problem in diabetic patients. 6 Thyroid hormones and insulin are the antagonistic, and involved in the metabolism of carbohydrates, proteins, and lipids. Thyroid hormone as well as insulin levels are altered if there is functional impairment of the thyroid gland and endocrine pancreatic beta cells. 7 Thyroid disorders adversely affect diabetes control. Diabetes Mellitus appears to influence thyroid function in two sites; firstly, at the level of hypothalamic control of TSH release and secondly at the conversion of T 4 to T 3 in the peripheral tissue. Increased hyperglycemia causes reversible reduction of the activity and hepatic concentration of T 4 -5?-deiodinase, low serum T 3 , increase in reverse T 3 and also variation in the level of T 4 . 8 Euthyroid Sick syndrome (ESS) or Non-thyroidal illness Syndrome (NTIS) identifies abnormalities of thyroid function tests observed in patients with systemic nonthyroidal illnesses and in those patients undergoing surgery or fasting. [9][10][11] Abnormalities of thyroid function tests observed in ESS or NTIS includes 1) Low T 3 Syndrome 2) Low T 3 and T 4 syndrome 3) High TT 4 syndrome 4) other abnormalities like low TT 3 and TSH, high TSH and low TT 3 and TT 4 . 12 A previous study among young Bangladeshi diabetic population demonstrated significant alteration of thyroid hormone pictures in absence of clinical thyroid diseases which is consistent with the other study done in abroad earlier. 22 But ESS or NTIS in the setting of type2 diabetes was not investigated extensively earlier and there is no available data regarding the changes in thyroid hormone pictures in patients with uncontrolled type2 Diabetes Mellitus among Bangladeshi population. Although there are few studies in abroad; which revealed that that there are significant alteration of thyroid hormones in uncontrolled type2 diabetic subjects. 19,20,23,24 As most of these studies did not exclude other causes of ESS or NTIS which are responsible for activating inner ring deiodination or inhibition of outer ring deiodination of T 4 to produce T 3 from T 4 instead of rT 3 ; 25 the result was found to be poorly representative.

In the above context our present study was designed to document the changes of thyroid hormones pictures in absence of clinical thyroid diseases among Bangladeshi population in the setting of uncontrolled type2 diabetes mellitus.

2 II.

3 Objectives and Methods

To evaluate the circulating thyroid hormone pictures in absence of clinical thyroid diseases among type 2 diabetic subjects in a group of Bangladeshi population.

4 III.

5 Methodology a) Types of study

This was a case and control study.

6 b) Place and duration of study

The study was conducted in the Endocrinology department of Sylhet MAG Osmani Medical College (SOMC) and Hospital, Sylhet, Bangladesh in collaboration with the Research Division, BIRDEM, Dhaka, Bangladesh during the period of January 2016 to December 2017.

7 c) Study population

A total of 100 type 2 diabetic subjects, 30-50 years of age, irrespective of glycemic status, duration of diabetes, BMI and sex were recruited from the outpatient department (OPD) of SOMC hospital and BIRDEM hospital. Prior to recruitment, diabetes mellitus was confirmed according to current American Diabetic Association (ADA) criteria for the diagnosis and classification of diabetes mellitus. 24 Control subjects (n=100) were selected from friends and family of the patients within 5 years of age band without diabetes or impaired glucose regulation (IFG, IGT) determined according to ADA criteria 24 and having no clinical thyroid diseases or other evident systemic diseases documented on clinical evaluation. Informed written consent was taken from all recruited diabetic and control subjects for the purpose of the study.

8 d) Exclusion criteria

? Type 2 diabetes with acute metabolic decompensation. Experiments on both animal and human models Diabetes Mellitus was found to be associated with alteration of thyroid hormone picture in absence of clinical thyroid diseases irrespective of the type of diabetes. In both type1 and type2 diabetes significant reduction of both TT 3 and FT 3 , increased rT 3 and high rT 3 /T 3 ratio was demonstrated. [13][14][15][16] Serum FT 4 and FT 4 I were normal, TT 4 was normal or suppressed and TSH was found normal or slightly elevated. 17,18 All the parameters of thyroid function specially TT 3 , FT 3 and rT 3 become normal when euglycemia was achived. 14,19,20 More over it was found that reduction of FT 3 and TT 3 , rise of rT 3 are significantly correlated with the severity of hyperglycemia and the thyroid secretory response to large dose of TSH is also declined in uncontrolled diabetes mellitus which frequently improves with improved glycemic control. 21

9 Medical

10 e) Method

Selection criteria as per availability and was given an appointment to come in a particular date. Preparation of the subjects and collection of blood of the Controls and diabetic subjects that were assigned for the purpose of study done according to the recommendation of the ”Report of the Expert committee of the Diagnosis and Classification of Diabetes Mellitus. 24 They were requested to fast overnight for at least eight hours and in the subsequent morning 16 ml of venous blood was drawn from the ante-cubital vein by using 25 cc disposable plastic syringe with 18G needle for the estimation of fasting serum insulin, C-peptide, glucose, HbAlc, TT 3 , TT 4 , FT 3 , FT 4 and TSH. One ml of collected venous blood was taken in an anticoagulant containing vial for estimation of HbAlc. Remaining 15ml of blood was kept in 3 separate plain test tubes in equal amounts (5ml in each) to centrifuge immediately. Blood sample contained in the test tube was centrifuged for 15 minutes at a rate of 4000 rpm. A total of 200 µl of serum was collected in appropriately labeled eppendorf in duplicate with the help of micropipette for each of the biochemical parameters. Then the serum sample was preserved immediately at -30° C for analysis.

11 f) History and clinical examination

Detailed socio-demographic and clinical data were recorded in a pre-designed case record form. These include age, sex, residing area, occupation, socioeconomic status, dietary habit, exercise, alcohol and smoking habit, duration of diabetes, associated diseases like hypertension, obesity, dyslipidemia, coronary artery disease, cerebrovascular diseases, peripheral vascular diseases and crystal deposition diseases. Family history of these diseases were also been noted. Classical and non-classical features of diabetes mellitus and any adverse outcome of diabetes on life style was noted by taking history from the diabetic subjects.

Hight, weight, BMI, waist circumference, hip circumference, waist hip ratio (WHR), waist height ratio (WHtR) of all the controls and diabetic subjects were recorded. Percent body fat and total fat mass was measured by "Body logic Body fat monitor; Omron Corporation, Japan". Systolic and diastolic blood pressure of all patients and control subjects was recorded. Blood pressure was measured by using mercury sphygmomanometer after at least 5 minutes of recumbence in a calm and quiet environment. Systolic blood pressure 130 mm Hg and the diastolic blood pressure 85 mm Hg was taken as the cut-off value for categorizing the normal and the abnormal values among diabetic population. 25

12 g) Statistical analysis

All the data were expressed as mean standard deviation, median (range) and/or number and percentage (%) as appropriate. Statistical analysis was done by using SPSS 7.5 packages for windows. Appropriate statistical test of significance like unpaired t test, one way analysis of variance (ANOVA) and Mann-Whitney test was used as necessary. $P < 0.05$ was taken as minimum level of significance.

13 h) Data presentation

Tabulation and / or drawing either in the form of graph or in the form of diagram were utilized as necessary for data presentation.

IV.

14 Results

Table

15 (BMI A=BMI upto 25). (BMI B=BMI 25.1-30). (BMI C=BMI>30) (P value was calculated by ANOVA Bonferrony, U/p value was calculated using Mann-Whitney U test)

Table-6 showed that when TT 3 , TT 4 , FT 3 , FT 4 and TSH were grouped according to BMI category and compared separately among control and Diabetic subjects in three BMI groups; no significant difference was observed.

16 Discussion

Some studies done earlier in abroad; the age (mean±SD) of type 2 diabetic patients who were participated in study was (47.5±7.4) years coincides with the fact that type 2 diabetes mellitus usually develops after the age 40 years. 9,26,27 . Where as in our study age (mean±SD) of the control and diabetic subjects were 39.5±5.2 and 39.2±5.8 respectively. Thyroid hormones among control and Diabetic subjects was evaluated and it was found that the differences observed in serum thyroid hormones and TSH levels between controls and diabetic subjects were not statistically significant. When the thyroid hormones and TSH were reevaluated on the basis of BMI and HbAlc groups among the diabetic subjects, similar observation was noted (table 5 and 6). But when serum TT 19, 20). This finding is consistent with the findings of the other studies done in abroad in both type 1 and type 2 diabetic subjects. [11][12][13][14][15][16][28][29][30][31] . Our findings showed that around the level of 12mmoll of fasting serum glucose was associated with marked alteration of thyroid hormone picture in the blood in absence of clinical thyroid diseases. When low TT 3 group was categorized according to BMI, diabetic subjects having BMI within normal range was found to have more deteriorating fasting serum glucose, HbA1c and serum TT 3 levels; compare to other BMI groups (Table -8). This finding suggests that changes in thyroid hormone possibly much more obvious in young diabetic groups who are mostly have low or normal BMI than the type2 diabetic subjects that are mostly associated with obesity and higher degrees of BMI. These findings also supports the findings of the others study done in abroad. 21 and also in the cell and molecular biology department of BIRDEM, Dhaka, Bangladesh. 22 Our findings also conclude that BMI and other indices of obesity possibly have very little or no impact on serum thyroid hormones and TSH levels until and unless they are associated with very high serum fasting glucose levels beyond 12mmol/l.

VI.

17 Conclusion

1. Uncontrolled type 2 diabetes mellitus is associated with alteration of thyroid hormone pictures particularly altering the TT 3 , FT 3 and TSH in absence of clinically evident thyroid diseases. 2. This biochemical feature is more evident if the BMI of the subjects is low or normal range and it was also found that the more worsening the glycemic status as determined by FPG and HbA1c, there was more deteriorating circulating serum thyroid hormone pictures and TSH. 3. Interpretation of abnormal thyroid hormone pictures requires a very high index

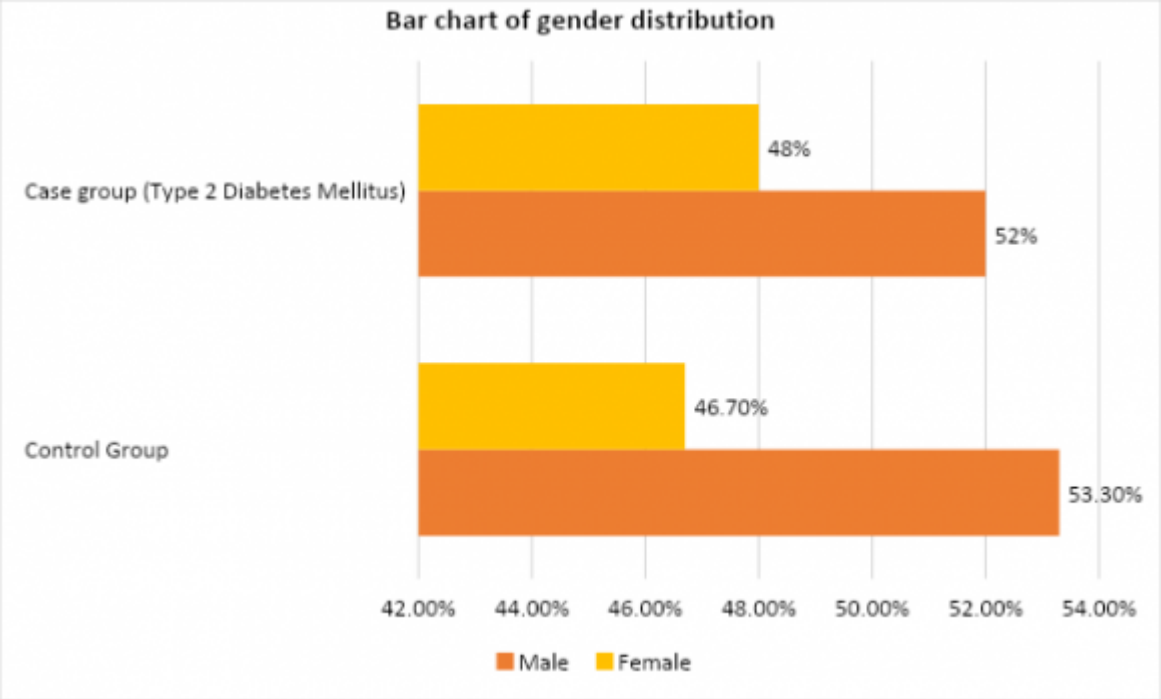

Figure 1:

1

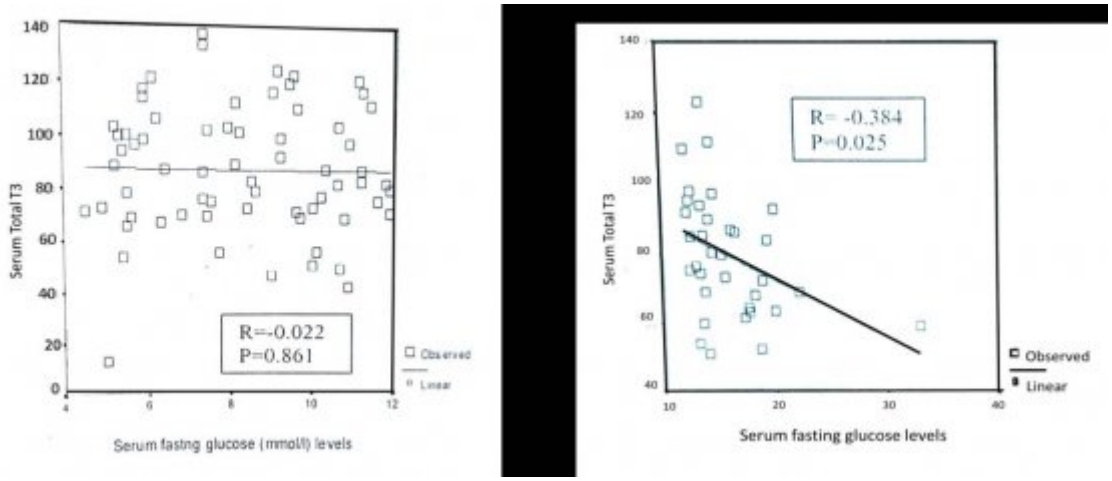

Figure 2: Figure- 1 :

Groups	Age mean ± SD	Annual Income Median (Range)	Family Member	SBP mean ± SD	DBP mean ± SD	Duration of DM, years
Controls (n =30)100	39.53± 5.24	120000 (30000-220000)	6 ±1	120 ±23	80±7	–
DM(n=100)	39.24± 5.79	100000 (20000-200000)	6± 2	124 ±17	80±10	0.02 (0.01-6)
t/p value		u/p value		t/p value		
Cont vs DM	-.248/0.804	1114/0.32*	1.1770/.241	1.177/0.241	1.101/0.273	

[Note: In table-1 shows demographic status of the study group where mean±SD age of the control and diabetic subjects were 39.5±5.2 and 39.2±5.8 respectively. Duration of diabetes is one month to six years. Systolic and diastolic blood pressure of the control and diabetic subjects were almost similar and it was within normal range. The table given below showed it in detail:]

Figure 3:

suspicion in patients with uncontrolled type2 diabetes mellitus as it was found to have associated with ESS or NTIS. [1]

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Alteration of Thyroid Hormone Pictures in Absence of Clinically Evident Thyroid Diseases among Type 2 Diabetic Subjects in a Bangladeshi Popula

H/O CVD	Present	0	0	06
Retinopathy	Present	0	0	35
Neuropathy	Present	0	0	35
Nephropathy	Present	0	0	25
Anti DM drugs	Present	0	0	24
Typical Symptoms	Present	0	0	37
Atypical Symptoms	Present	0	0	63

Table-3: Thyroid hormone status in diabet

Parameters	MC**	Control	DM	TC**	MD**	FD**	TI
TT 3	93.67±	FC**					
TT 4	17.14	83.46					
FT 3	8.54±	±12.78					
FT 4	1.9	8.07±					
TSH	2.69	1.31					
	±0.36	2.56					
	1.49	±0.55					
	±0.21	1.37					
	±	±0.23					
	0.88	±1.16					
	1.33	1.35					

Controls In table-3 shows thyroid hormone status in diabetic and control subjects. Mean±SD of TT3; (ngm

No Exercise Smoker Groups Non Smoker Groups with Low level of Thyroid hormone Smoking Past Smoker Absent Table-4 showed that the mean serum TT3 in patients with low T3 syndrome groups of patients and

	Absent	76	76	50
H/O CAD	Present	4	4	38

*[Note: **(MC=Male control, FC= Female Control, TC= Total Control, MD=Male Diabetic, FD= Female Diabetic, TD=Total Diabetic)]*

Figure 4: Table - 2

4

Table-5: Thyroid hormone pictures in diabetic subjects according to HbA1c

Groups	TT 3	TT 4	FT 3	FT 4	TSH	FPG	HbA1c	S Insulin	S C P
Group A, N=13	78.42±	8.77±	2.40	1.37±	1.37±	5.97±	6±	5.9 (3.5-12.5)	0
	24.50	1.15	±0.59	0.25	0.25	1.8	0.56		(5
Group B, N=15	89.71±	8.00	2.35±	1.22±	1.90±	7.7±	7.37±	8.0 (3.2-16.3)	0
	24.33	± 1.53	0.61	0.27	1.40	1.9	0.32		(2
Group C, n=72	84.19	8.45	2.35±	1.39±	1.41±	12.39±	10.84±	7.9 (19-48.9)	0
	±21.51	±1.95	0.73	0.24	1.11	4.5	1.89		(3
			P value					U/p value	
A vs B		0.554	0.773	0.255	0.774	0.135	0.749	0.09	75/0.30	8
A vs C		1.000	1.000	1.000	1.000	1.000	0.000	0.000	343/0.13	3
B vs C		1.000	1.000	1.000	0.97	0.862	0.000	0.000	513/0.76	4

(Group A=HbA1c < 7%, Group B=HbA1c 7%-8%, Group C=HbA1c > 8%)

(P value was calculated using one way analysis of variance, U/p value was calculated using Non-parametric

Figure 5: Table 4 :

6

Groups	Serum Insulin	Serum C peptide	FPG mg/dl	HbA1c%	TT 3	TT 4	FT 3	FT 4	TSH
BMI A	6.0 (1.9-38.0)	0.74(0.06-3.62)	11.77±5.18	10.35±2.63	81.45	8.51±	2.31±	1.41±	1.28
N=55					±20.70	1.77	0.68	0.26	±0.8
BMI B	8.6 (2.3-48.9)	0.76(0.12-5.11)	9.66±3.79	8.83±2.01	89.54±	8.46±	3.02±	1.32±	1.78
N=35					24.58	1.78	2.72	0.26	±1.5
BMI C	14.9 (4.9-21.5)	0.94(0.20-2.13)	9.96±3.30	9.10±2.01	81.33±	7.74±	2.00±	1.29±	2.09
N=10					20.62	2.15	0.56	0.18	±1.3
	u/p value			P Value					
A Vs B	710/0.036	811/0.21	0.108	.013	0.285	1.000	0.164	0.721	0.160
A vs C	140/0.014	219/0.30	0.761	.399	1.000	1.000	1.000	0.651	1.000
B vs C	120/0.13	172/0.93	1.000	1000	0.913	1.000	0.288	1.000	1.000

Figure 6: Table 6 :

7

Groups		FPG	HbA1c	BMI	% body Fat	Total Fat Mass	Fasting S
BMI A	Low T 3	14.24±7.13	10.74±3.15	23.16±1.39	23.46±5.45	7.6 (1.92-18.3)	7.6 (1.
	Normal T 3	1018±3.61	10.18±2.39	22.74±1.89	25.48±5.84	5.55 (1.9-38.0)	5.55 (1
	t/p value	1.96/0.064	0.721/0.474	0.813/0.420	-1.210/0.23	u/p value	u/p valu
BMI B	Low T 3	9.55±4.40	9.08/±2.41	27.19±1.25	33.31±4.83	8.0 (2.3-47)	8.0 (2
	Normal T3	9.70±3.68	8.76±1.27	27.33±1.45	3.72±5.82	8.8 (3.5-48.9)	8.8 (3
	t/p value	-.094/0.925	0.380/0.706	-0.233/0.817	1.146/0.26	u/p value	u/p valu
BMI C	Low T 3	10.45±0.64	9.55±1.34	33.41±3.61	36.85±6.29	13.4 (5.3-21.5)	13.4 (5
	Normal T 3	9.84±3.73	8.99±2.35	34.63±1.60	37.30±4.10	14.9 (4.9-20.8)	14.9 (4
	t/p value	0.222/0.83	0.294/0.776	1.144/0.286	-.182/0.901	0.335/0.726	u/p valu

(BMI A=BMI upto 25). (BMI B=BMI 25.1-30). (BMI C=BMI>30)

Figure 7: Table 7 :

8

	Groups	FPG	HbA1c	Fasting S. Insulin	BMI	%Body Fat	Total Fat Mass
TT 3	LowTT 3 (n=27)	12.57±6.44	10.16±2.89	7.7(1.9-47.0)	25.11±3.35	27.37±3.74	18.12±5.93
	Normal TT 3 (n=73)	10.21±3.63	9.52±2.32	8(1.9-48.9)	25.41±3.45	28.72±6.83	19.14±6.13
	t/p value	2.30/0.024	1.572/0.119	1972/0.92*	-0.384/0.702	-0.856/0.394	-0.753/0.453
FT 3	LowFT 3 (n=12)	11.45±5.09	9.98±2.43	7.4(4.4-38.0)	26.59±3.52	30.42±7.24	21.42±5.94
	Normal FT 3 (n=88)	10.77±4,61	9.66±2.51	7.8(1.9-48.9)	25.16±3.33	28.07±6.91	18.52±6.03
	t/p value	0.475/0.636	0.426/0.671	480.5/0.61*	1.357/0.178	1.096/0.276	1.562/0.122
TSH	Low TSH (n=12)	12.24±4.16	10.86±2.48	8.3(1.9-48.9)	25.27±1.82	30.19±7.65	19.98±5.0
	Normal TSH (n=88)	10.81±4.78	9.65±2.48	7.7(1.96-47.0)	25.21±3.65	27.63±6.66	18.40±6.20
	t/p value	0.986/0.327	1.573/0.137	461.5/0.48*	0.449/0.218	1.524/0.782	0.982/0.624

Figure 8: Table 8 :

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Figure 9: Table - 8

[Note: group and TSH with low values of thyroid hormones groups and TSH among the diabetic subjects, 27 diabetic patients were found to have low TT 3 below the lower limit of normal range than that of their normal counterpart which was significant at p=0.0001 level (table-4 and 8), 12 patients were found to have serum]

Figure 10:

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