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Dysglycemia and dyslipidemia in Type 2 Diabetes Mellitus in co-morbidity with Hypothyroidism

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Abstract: *Background:* Hypothyroidism is commonly associated with Diabetes Mellitus Type 2, and can affect glycemic control and alteration of lipid profiles with increase in the downstream end-organ related morbidities. *Objectives:* To find the changes in parameters of glucose and lipid metabolism in Diabetes Mellitus Type 2 in presence of hypothyroidism before and after replacement therapy with L-thyroxine. *Methods:* In consecutively diagnosed new patients with Diabetes mellitus Type 2, Thyroid screening was done viz. T3, T4, TSH, fT3, fT4. Then Fasting Plasma glucose (FPG), HbA1c, Total Cholesterol (TC), Triglycerides (TG), Very low-density cholesterol (VLDL), Low-density cholesterol (LDL), High-density cholesterol (HDL) were compared among two study groups viz. in Diabetics with hypothyroidism (n=50) and Diabetics without hypothyroidism (n=50) before and after thyroxine replacement and metabolic parameters were analyzed in relation to euthyroid-euglycemic Control group of healthy volunteers. *Results:* Mean FPG and HbA1c were significantly higher in Diabetics in presence of hypothyroidism compared to euthyroid diabetics. Lipid profiles were also noted to have been compromised in Diabetics in presence of hypothyroidism. After achievement of euthyroid status and with management of diabetes, diabetics achieved significantly reduced FPG and HbA1c along with significantly normalised lipid profile echelons. *Conclusion:* Our study suggested that we should have high index of suspicion of association of hypothyroidism in diabetics. We need to improve systems approach of routine thyroid screening as Standard Operative Procedure in patients with Diabetes Mellitus Type 2.
Keywords: Dysglycemia, Dyslipidemia, Diabetes Mellitus Type 2, Hypothyroidism

Introduction

Diabetes mellitus Type 2 (DM) is the commonest endocrine disorder, with thyroid dysfunction being the second among human population. Thus there is factual need to appraise the potential interrelationship between these two frequent morbidities [1]. In the past millennium, the Dundee research group reported closely linked epidemiological association between DM and thyroid dysfunction supported later by other researchers [2-3].

Literature reports increase of asymptomatic thyroid dysfunction in the diabetic population in last few decades [4-5]. “Diabetic dyslipidemia” is a known identity with higher levels of triglyceride (TG) along with low-density lipoprotein (LDL) and lower levels of high-density lipoprotein (HDL) in plasma. Research groups postulated this by the compromised action of insulin with or without insulin resistance at the end-organ levels increasing risk of the cardiovascular diseases [6-7] Researchers also noted that dyslipidemia in hypothyroidism (HY) with coexisting metabolic alterations were closely linked with Diabetes mellitus [8-11].

In the above scenario, the researcher noted that intervention of dysglycemia and co-existing dyslipidemia is not possible without evaluating thyroid status of the diabetics. For the early diagnosis, and healthier outcomes in diabetics, we need to assess thyroid co-morbidity. Clinical Practice Guidelines may need thyroxine replacement in management of diabetes in presence of hypothyroidism which can reverse both dysglycemia and dyslipidemia earlier to delay complications with better prognosis. The present study was conducted to find dysglycemia and dyslipidemia among newly diagnosed cases of

Diabetes mellitus Type 2 with co-morbidity of hypothyroidism before and after replacement with levothyroxine.

Material and Methods

This hospital based open-level cross-sectional study on dysglycemia and dyslipidemia was conducted on newly diagnosed patients with hypothyroidism and Diabetis mellitus Type 2 at the Department of Biochemistry in collaboration with Department of Medicine in a tertiary care teaching hospital in eastern India. This study was undertaken as self□funded project within the range of the academic activities supervised by and under mentorship of the faculty members of the departments as part of post-graduate training.

Inclusion Criteria: Consecutive newly diagnosed adult patients from outpatients department pursuing domiciliary treatment were recruited in this study into four groups viz. Hypothyroidism only (HY; n=50); Diabetes mellitus Type 2 only (DM; n=50); diagnosed with both ailments simultaneously (HY+DM; n=50); age and gender-matched apparently healthy caregivers without any history or symptoms suggestive of morbidity affecting dysglycemia or dyslipidemia as the euthyroid-euglycemic Control (C; n=50).

Exclusion Criteria: Exclusion criteria were persons less than 18 years and suffering from or had indicative symptoms of diabetes and thyroid disorders; any other diagnosed endocrinal and metabolic disorders, pregnancy; acute and chronic co-morbidities, viz. infection, febrile illness, Sickle cell anaemia and hemoglobinopathies, Thyroiditis, hypothyroidism from post-thyrodectomy or radiotherapy;, benign or malignant disorders, transplant rejection, hypertension and cardiovascular diseases, gastro-intestinal and central nervous system diseases, renal disease with or without failure, diabetic or thyroid crisis, hepatic dysfunction, inflammatory bowel diseases. Further, persons on antioxidant supplementation or lipid lowering drugs, aspirin, vitamin C or steroid therapy; smokers were excluded from the study.

Data Collection Procedure: The study conformed to the Helsinki Declaration. Institutional Ethics Committee approved the study and permissions were taken from concerned authorities prior to commencing recruiting participants. Informed consent process was pursued in letter and spirit. The participants were individually explained of all the procedures that no harm is expected to them during participation in the study and they can leave the study at any point of time without showing any reason. They were promised that no financial or other forms of coercion or negligence will be imposed on them whether they agree to participate in this study or not. The researcher of this study showed indebtedness to the participants as their cooperation helped us complete the study. Then written informed consents were obtained from all the individuals individually before participation.

The participants were provided option and choices to pursue their treatment as per their schedules and regular lifestyles during this study including drug intake and dietary habits. All the patients were from comparable socioeconomic, cultural and lifestyle standing and voluntarily participated in the study as cases and controls. The participants of the study underwent all other relevant investigations and data regarding patients were documented and data protection was ensured. The sanctity and secrecy of the data was maintained.

Operational Technical Information: For these biochemical studies, fasting non-haemolysed blood sample was collected after a minimum of 12 hours of fasting and used, except for the postprandial plasma glucose estimation. Blood was collected from the antecubital vein, following universal precautions. The sample was then allowed to clot in the aliquot at room temperature for about 2 hours and was then centrifuged at 3000 rpm for 10 minutes to separate the serum.

DM was diagnosed on the WHO criteria, i.e. fasting plasma glucose 126 mg/dl (7.0 mmol/L) With symptoms of diabetes and 2 hour postprandial plasma glucose level of 200 mg/dl (11.1 mmol/L) or more, for which sample was drawn 2 hour following ingestion of 1.75 g per kg body weight with a maximum of 75 g of oral glucose in 300 mL of water. [12]. Fasting and postprandial plasma glucose was estimated quantitatively using GOD/POD technique as described by Trinder [13].

Serum free T3 (fT3), T4 (fT4), TSH were estimated quantitatively using chemiluminescent assay technique [14]. HbA1C was estimated from the whole blood by ion-exchange high-performance liquid chromatography using Bio-Rad D10 HbA1c program certified by National Glycohemoglobin Standardization Program [15]. Total cholesterol (TC) was quantitatively assessed by CHOD-PAP technique as depicted by Allian [16]. Triacylglycerol was quantitatively assessed by GPO-ESPAS technique as illustrated by Bucolo and David [17]. HDL was quantitatively assessed by the PEG-PAP method [18]. The LDL level was not measured directly, instead this was estimated using Friedewald formula [19-20].

Data Analysis: Data was analysed using statistical software IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY and GraphPad Prism 7.1, 2018 GraphPad Software, Inc. (Trial version) All results were summarized as mean ± SEM. Two-way ANOVA significance test done with Bonferroni post-tests to compare replicate means by row, each column to all other rows; the comparison between cases and control was done by using Student's t-test. The difference was considered to be statistically significant an alpha error level of less than five percent.

Results

In this study on the consecutive newly diagnosed study participants with Diabetes mellitus Type 2, Thyroid screening was done followed by analysis of dysglycemia and dyslipidemia pre- and post-thyroxine replacement in relation to euthyroid-euglycemic Control group [Table-1 & Table-2].

Table-1: Dysglycemia compared to Controls before and after replacement therapy in Overt hypothyroidism, with Type 2 Diabetics, with Both hypothyroidism & Type 2 Diabetes

Variable	Overt hypothyroid HY Mean± SEM		Overt hypothyroid & Type 2 Diabetes Mean± SEM		Control Mean± SEM	ANOVA with test significance: p value					
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment		HY Pre-treatment vs. Control	HY Post treatment vs. Control	HY Pre-treatment vs. Post treatment	HY + DM Pre-treatment vs. Control	HY + DM Post treatment vs. Control	HY + DM Pre-treatment vs. Post treatment
FPG (mg/dl)	87.2 ± 7.8	87.8 ± 1.8	206 ± 5.81	115 ± 4.76	89.1 ± 6.11	>0.05	>0.05	>0.05	<0.001	<0.001	<0.001
PGPG (mg/dl)	106.8 ± 4.1	105.8 ± 2.1	219.8 ± 4.1	139.8 ± 2.1	111.6 ± 12.1	>0.05	>0.05	>0.05	<0.001	<0.001	<0.001
HbA_1C (%)	6.60 ± 2.27	4.89 ± 1.9	9.13 ± 0.51	5.83 ± 1.11	4.34 ± 0.03	<0.001	>0.05	<0.001	<0.001	<0.001	<0.001
TSH (µ IU/ml)	10.93 ± 2.11	3.61 ± 1.18	13.73 ± 3.71	5.71 ± 1.28	2.93 ± 1.23	<0.001	>0.05	<0.001	<0.001	<0.001	<0.001
T4 (µg/dL)	5.29 ± 1.9	8.21 ± 3.4	4.18 ± 2.9	8.17 ± 3.14	8.12 ± 0.78	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
fT4 (ng/ dL)	0.97 ± 0.41	1.43 ± 0.4	0.73 ± 0.49	1.09 ± 0.33	1.4 ± 0.76	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
T3 (ng/ dL)	95.4± 11.84	124.8 ± 44.13	98.4 ± 11.44	126.8 ± 44.13	161.4 ± 12.97	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
fT3 (pg/mL)	1.42 ± 1.23	2.92 ± 1.23	1.38 ± 1.02	2.84 ± 1.72	2.92 ± 1.81	<0.001	>0.05	<0.001	<0.001	>0.05	<0.001

*Bonferroni post-tests to compare replicate means by row, each columns to all other rows

Table-2: Dyslipidemia compared to Controls before and after replacement therapy in Overt hypothyroidism, with Type 2 Diabetics, with Both hypothyroidism & Type 2 Diabetes

Variable	Overt hypothyroid HY Mean± SEM		Overt hypothyroid & Type 2 Diabetes Mean± SEM		Control Mean± SEM	ANOVA with test significance: p value					
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment		HY Pre-treatment vs. Control	HY Post treatment vs. Control	HY Pre-treatment vs. Post treatment	HY + DM Pre-treatment vs. Control	HY + DM Post treatment vs. Control	HY + DM Pre-treatment vs. Post treatment
TC	267.38±7.74	262.48±6.23	277.92± 9.79	269.78±8.89	199.26±9.69	<0.001	<0.001	>0.05	<0.001	<0.001	<0.001
TG	249.46±9.43	243.42±2.83	250.02± 7.14	247.02±8.84	195.43±3.23	<0.001	<0.001	<0.001	<0.001	<0.001	>0.05
LDL	182.69±9.66	178.61±8.33	186.17± 7.09	179.77±6.69	156.01±7.43	<0.001	<0.001	>0.05	<0.001	<0.001	<0.001
VLDL	49.29±7.56	44.22±6.33	51.01± 8.02	48.41± 9.82	39.25± 8.87	<0.05	<0.001	<0.05	<0.001	<0.001	>0.05
HDL	41.20±5.36	44.21±6.86	42.74± 7.29	45.84± 8.49	48.13± 9.65	<0.001	>0.05	>0.05	<0.01	>0.05	>0.05

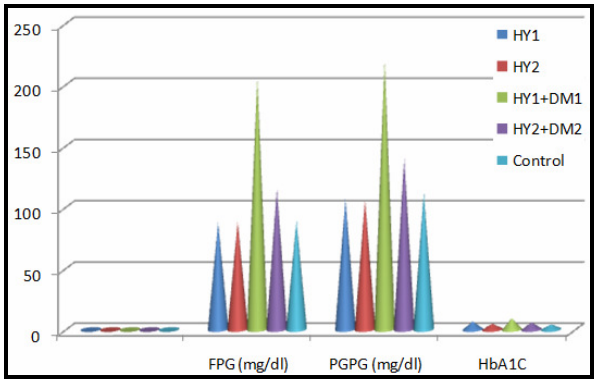
*Bonferroni post-tests to compare replicate means by row, each columns to all other rows

In co-morbid conditions with both hypothyroidism and diabetes (HY + DM):

Dysglycemia:

Fasting Plasma Glucose (FPG), Post-Glucose Plasma Glucose (PGPG), Glycated haemoglobin (HbA1C): These values were highly significant before and after thyroxine replacement ($p<0.0001$) and also when the values were compared to controls [fig-1].

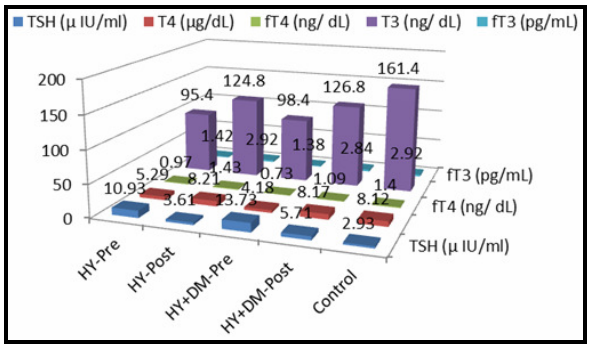
Fig-1: Dysglycemia



Thyroid Profiles:

Thyroid Stimulating Hormone (TSH), Triiodothyronine (T_3): In co-morbid conditions (HY + DM), these values were highly significant before and after thyroxine replacement ($p<0.0001$) and also when both values were compared to controls [fig-2]

Fig-2: Thyroid profile

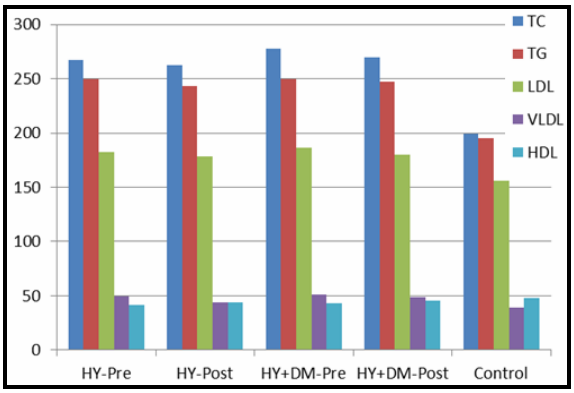


Free Triiodothyronine (fT_3): These values were highly significant in co-morbidities before and after thyroxine replacement ($p<0.0001$) and in before only when compared to controls.

Dyslipidemia:

Total Cholesterol (TC) and Low density lipoprotein (LDL): These values were highly significant before and after thyroxine replacement ($p<0.0001$) and also when both values were compared to controls [fig-3].

Fig-3: Dyslipidaemia



Triglycerides (TG) and Very low density lipoprotein (VLDL): These values were highly significant before and after thyroxine replacement ($p<0.0001$) only when were compared to controls; not among themselves.

High density lipoproteins (HDL): These values were highly significant before thyroxine replacement ($p<0.0001$) only when were compared to controls.

In only hypothyroid morbidities (HY):

Dysglycemia:

FPG, PGPG: No significant differences were noted.

HbA1C: These values were highly significant before and after thyroxine replacement ($p<0.0001$) and in before only when compared to controls.

Thyroid profiles:

T_3: The values were highly significant before and after thyroxine replacement ($p<0.0001$) and also when both values were compared to controls.

TSH and fT_3: These values were highly significant before and after thyroxine replacement ($p<0.0001$) and in before only when compared to controls.

Dyslipidemia:

TG: These values were highly significant before and after thyroxine replacement ($p<0.0001$) and also when both values were compared to controls.

TC and LDL: These values were highly significant before and after thyroxine replacement ($p<0.0001$) only when both values were compared to controls.

VLDL: These values were highly significant after thyroxine replacement ($p<0.0001$) only when both values were compared to controls.

HDL: These values were highly significant before thyroxine replacement ($p<0.0001$) only when both values were compared to controls.

Thyroxine (T_4) and Free Thyroxine (fT_4): Incidentally, neither any significant difference was noted in hypothyroid or in co-morbidities with both hypothyroidism and diabetes.

Discussion

In our study, detailed clinical evaluation for Thyroid and Diabetic status done on all participants was done during study while they were on standard treatment protocol and lifestyle management. Our result showed that there was significant difference with the independent and dependant variables in terms of glycemic control and lipid profile when both Thyroid disorders and DM were present as co-morbidities or not.

Literature supports role of Thyroid hormones to boost glucose absorption, production, and utilization. Further, diabetic morbidities are unfolded by hyperthyroidism and dysglycemia by hypothyroidism. Conversely, Diabetes influence thyroid at levels from hypothalamic control of TSH, thereby release of T3 and assembly of T4 in the target organs to lower circulating T3 level. [21-22].

Further, in addition to genetic link of thyroid and DM ailments, former also have documented effects on glucose and lipid metabolism interacting with the regulatory network for energy homeostasis and insulin to regulate glucose clearance in the peripheral tissues [23]. Other research groups are in concurrence with our observation on lipoprotein alterations among patients suffering from HY, DM and having both these chronic morbidities. They also recognized the role of treatment of thyroid disorders among DM benefit glycemic control to attenuate cardiovascular risk, and thereby improvement of general well-being [24-25].

Our observation on HbA1c was supported by other research groups. The Korean study observed levels of HbA1c to be spuriously high in non-diabetic patients with overt hypothyroidism [26]. Recent Indian study also concluded that the L-thyroxine replacement therapy have been able to reduce HbA1c values & mean HbA1c after reaching euthyroid status in hypothyroid patients [27]. Another Indian study reported that HbA1c level was falsely elevated in hypothyroidism, out of proportion to glycemia that dropped without any change in plasma glucose after hypothyroidism tweak [28].

Strengths of the study: Firstly, we evaluated counterfeit diagnosis of dysglycemia directing intervention of frank Diabetes, in under-diagnosed hypothyroidism. Secondly, to the horizon of our knowledge, this was the pioneering study in this part of India to correlate the dysglycemia and dyslipidemia in patients with diabetes and healthy controls in relation to presence or absence of thyroid deficiency cases.

Limitations of the study: We had several limitations that included smaller sample size of our study population and open label design. Further, selection bias also limited the generalizability of our findings since only the subjects from our diabetic clinic were sampled.

Future directions of the study: Our findings further goes to say that we may have to do a study in primary cases of diabetes, conduct a comparative study among different ethnic groups and polymorphism in the population before we can establish the role of hypothyroid in diabetics. This study intended to look for thyroid dysfunction in diabetic patients to find the correlation between thyroid hormones and dysglycemia which needs to be further established by prospective population-based studies. These profiles of

TY and DM patients in our hinterland matched with some of the observations of our global peers that need to corroborate by robust multicentric study across regions.

Conclusions

The observations of our study suggested that there is an urgent need to sensitize ourselves to improvise clinical practice guidelines of regular screening for thyroid status in all cases diagnosed with Diabetes Mellitus Type 2. Further, in all levels of health care education and capacity building, there is need of this modification in the Standard Operative Procedure regarding management of patients diagnosed with Diabetes Mellitus.

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