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Effect of Thyroid Hormone Levels on Glycemic Control: The Indian Context

Vatsal Navin Jain[1], Swati Ghanghurde[2], Sherwin Rajesh Carvalho[1], Shivani Sachin Nirgudkar[1], Mohit Vijay Rojekar[3]

[1]MBBS. Student, Rajiv Gandhi Medical College, Kalwa, Thane, Maharashtra, India.
[2]Assistant Professor, Department of Pathology Rajiv Gandhi Medical College, Kalwa, Thane, Maharashtra, India.
[3]Professor & Head, Department of Biochemistry Rajiv Gandhi Medical College, Kalwa, Thane, Maharashtra, India.

Abstract

Objective: Diabetes mellitus (DM) is known as the silent pandemic. It is hypothesized that other endocrine systems are affected by the metabolic changes occurring due to DM. We aimed to investigate the correlation of thyroid hormones with glycaemic and lipid parameters.

Materials and Methods: 81 diabetic patients and 81 non-diabetic age and sex-matched healthy volunteers participated in the study. Their blood samples were analysed for fasting blood glucose (FBG), glycosylated haemoglobin (HbA1C), total tri-iodothyronine (T3), total thyroxine (T4), free T3 (FT3), free T4 (FT4), thyroid-stimulating hormone (TSH), total cholesterol (CHOL), High-Density-Lipoprotein cholesterol (HDLC) and Low-Density-Lipoprotein cholesterol (LDLC). Data was analysed using appropriate statistical tests.

Results: Among the cases, 70.37% were euthyroid, while 24.7% had subclinical hypothyroidism, 2.47% had clinical hypothyroidism, 1.23% had subclinical and 1.23% had clinical hyperthyroidism. FBG, HbA1c and TSH ($P< 0.05$) were significantly higher in diabetics compared to controls. On the other hand, T3, FT3, FT4, and HDLC ($P< 0.05$) were significantly lower in diabetics compared to controls. A significant negative correlation ($P< 0.05$) was found when T3 and FT3 were compared against age, FBG and HbA1c. A significant positive correlation ($P< 0.05$) was found when T3 and FT3 were compared against HDLC, LDLC & CHOL.

Conclusion: Our statistics show that high-normal levels of T3 and FT3 are correlated with lower levels of FBG and HbA1c, hence improved glycaemic control. We recommend that thyroid profile of diabetic patients with poor control should be monitored regularly. Early detection of thyroid dysfunction and initiation of therapy for it, can improve the treatment outcome of hypoglycaemic drugs.

Keywords: Thyroid hormones, Hypothyroidism, Diabetes mellitus, Glycated haemoglobin A

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Corresponding Author:
Mohit Vijay Rojekar, Professor & Head, Department of Biochemistry Rajiv Gandhi Medical College, Kalwa, Thane, Maharashtra, India
Tel: (91) 839 046 5676
Email: mohitrojekar@gmail.com
Orcid ID: 0000-0002-8870-9182

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Introduction

Diabetes mellitus (DM), the silent pandemic (1), is a metabolic syndrome characterized by abnormalities involving interference in the normal function of insulin, which result in hyperglycemia. Complications of DM arise essentially from hyperglycemia (2). Hence, treatment of DM revolves around achieving glycaemic control. Thyroid function assumes significance in DM as studies have found that lower levels of serum tri-iodothyronine (T3) were linked to higher amounts of glycosylated haemoglobin in the blood, indicating poor glycaemic control (3,4). It can thus be extrapolated that if thyroid hormone levels are monitored and dysfunction is corrected during treatment of DM, better glycaemic control can be achieved and the risk of developing complications will be reduced (5). Some studies show that treatment of thyroid abnormalities significantly increases insulin sensitivity (6). It has been found that thyroid dysfunction also worsens as complications of DM appear (7); in fact, subclinical hypothyroidism may be associated with increased risk of microvascular complications of DM (6).Thyroid dysfunction is more common in diabetic females than in males (8,9); Hence, if the same is confirmed, then we suggest that current management regimes should be modified to monitor thyroid profile and watch out for subclinical conditions.

Thyroid hormones have a profound effect on the metabolism of macronutrients. Insulin and thyroxine are antagonistic to maintenance of blood glucose levels (10), which sounds paradoxical while higher levels of thyroid hormones should increase blood glucose (as hyperthyroidism results in hyperglycemia), they have been correlated with better glycaemic control in diabetic patients. However, correlation does not mean causation, and molecular mechanisms must be explored further.

We hypothesize that high-normal circulating levels of total T3 and free T3, potentiate the action of insulin, thereby increasing insulin sensitivity. This would help to achieve euglycemia by cellular consumption of glucose, halting the excess synthesis of ketones and cholesterol. Improved glycaemic control and normal levels of cholesterol would help to reduce the microvascular complications of DM.

Our study's scope covers correlations between routinely measured parameters for evaluating glycaemic control, thyroid function and lipid profile control. Our primary aim was to investigate the effects of thyroid hormones on glycaemic control and lipid profile in the Indian population. We also aimed to investigate whether significant differences exist between diabetic and non-diabetic subjects regarding these parameters.

Materials and Methods

The study was conducted between March 2021 and July 2021.

Diabetic subjects were selected conveniently from the cases presenting to various Out-Patient Departments and wards of a Medical College and tertiary healthcare centre in the Mumbai Metropolitan Region of the state of Maharashtra, India. Written informed consent was taken from the subjects in their preferred language prior to blood collection.

A minimum sample size was calculated using a modified version of Cochrane's formula on https://clincalc.com/stats/samplesize.aspx. Considering the incidence rate of thyroid dysfunction of 31% and 9.9% in the diabetic and non-diabetic population respectively (9,11), type-1 error as 5% and power as 90%, required sample size comes out to be 75 cases and 75 controls. Therefore, taking into consideration attrition rate of 10%, final sample size was 81 cases and 81 controls. The study sample consisted of 81 patients of Type 2 DM (42 male [M] and 39 female [F]) and 81 age and sex-matched non-diabetic, healthy volunteers. All patients had been previously

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diagnosed according to the standard American Diabetes Association (ADA) guidelines. The female subjects included those in the reproductive age group who were not menstruating at the time of sample collection, and post-menopausal women.

Inclusion criteria for the cases were: previously diagnosed adult patients suffering from type-2 DM with known or unknown history of thyroid dysfunction. Inclusion criteria for the controls were: non-diabetic adult volunteers in good health, not suffering from any overtly clinical thyroid or other endocrine dysfunction. The main exclusion criteria for both cases and controls were: pregnancy, presence of active microbial infection, unable to give informed consent by self (e.g. comatose, suffering from a serious disability, etc.), and age below 18 years.

The patients' basic medical history was taken, regarding their age/sex, medication regimen, and history of DM and other known disorders. A fasting blood sample was collected using standard venepuncture procedure and analysed for fasting blood glucose (FBG), glycosylated haemoglobin (HbA1c), total triiodothyronine (T3), free triiodothyronine (FT3), total thyroxine (T4), free thyroxine (FT4) and thyroid-stimulating hormone (TSH), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC).

We classified the subjects based on the results of their thyroid profile as euthyroid or suffering from subclinical and clinical hypo- and hyper-thyroidism.

Blood glucose (FBG) and lipid profile (CHOL, HDL, and LDL) were all analysed by photometric methods on Erba XL-640 automated analyser. Thyroid profile (T3, T4, FT3, FT4 and TSH) was analysed by chemiluminescence immunoassay (CLIA) on Biolumi 8000. HbA1c was measured using high performance liquid chromatography (HPLC) method on Erba Hb-Vario analyser.

The reports of the blood tests as well as the patient histories were carefully recorded using Microsoft Office Excel 2016 spreadsheet software. The data was further analysed on IBM SPSS version 26 software. Then, the parameters were tested against each other using paired T-tests and their Pearson correlation coefficients and *P* were calculated, and T-tests were used to analyse the data on SPSS.

Ethical considerations

A proposal to conduct this analytical cross-sectional study was submitted to the Institutional Review Board (IRB) and the Institutional Clinical Ethics Committee (ICEC). Both managements (IRB and ICEC) approved the proposal. The Ethics Committee approval letter number is RGMC/CSMH/ IEC/A/2021/03/185.

Results

Our study subjects varied in age from 29 years to 79 years (males) and 35 years to 85 years (female). The mean age (±SD) of males was 57.64 (± 10.74) years and 57 (± 11.72) years in females.

Among the 81 cases (42 M, 39 F), 70.37% were euthyroid (30 M, 27 F), while the rest (29.63%) had thyroid dysfunction. The categories of dysfunction, were subclinical hypothyroidism (24.7%; 10 M, 10 F), clinical hypothyroidism (2.47%; 1 M, 1 F), and subclinical (1 M) and clinical (1 F) hyperthyroidism (1.23% each). Out of the 20 cases of subclinical hypothyroidism and 2 cases of clinical hypothyroidism, only 2 (both subclinical hypothyroidism) were previously aware of their condition. 18 patients were diagnosed with subclinical hypothyroidism and 2 patients were diagnosed with clinical hypothyroidism during this study.

Among the 81 controls (42 M, 39 F), 90.12% (38 M, 35 F) were euthyroid, while the rest (9.88%) had only one form of thyroid dysfunction - subclinical hypothyroidism (4 M, 4 F). Out of the 8 cases of subclinical hypothyroidism, only 2 were previously aware of their condition. 6 cases were diagnosed during this study.

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The incidence rates of thyroid dysfunction in the diabetic and nondiabetic populations, 29.63% and 9.88%, closely resembled the numbers found in the literature and meta-analyses (9,11).

All the parameters were found to be distributed normally. Histograms were analysed and found to be reliable using Shapiro-Wilk test.

The parameters were tested to check if there was a significant difference in the test parameters between the cases and controls using independent samples T-test. The samples were grouped as cases (diabetics) and controls (healthy volunteers).

Levene's test for equality of variances showed that there was significantly higher variance of all parameters except HDL in diabetics, as compared to controls. Based on the results of this test, equality of means was tested by assuming equal variances (between diabetics and controls) for HDL and unequal variances for the other parameters.

The T-test for equality of means showed that there was a significant difference between cases and controls in the mean values of FBG, HbA1c, T3, FT3, FT4, TSH, and HDL. FBG, HbA1c, and TSH were significantly higher in diabetics compared to controls. On the other hand, T3, FT3, FT4, and HDL were significantly lower in diabetics compared to controls. However, mean values of T4, CHOL, and LDLwere not significantly different between the two groups as seen in Table 1.

Statistically, a significant correlation was found between T3/FT3 and indicators of glycaemic control (FBG and HbA1c). The correlation between T3 & FBG, FT3 & FBG and FT3 & HbA1c was significant at the 0.01 level, while the correlation between T3 & HbA1c was significant at the 0.05 level. All of these correlations are negative, implying that higher levels of T3 and FT3 corresponded to lower blood glucose and therefore, better glycaemic control as shown in Table 2.

The correlation between T4 and glycaemic markers was not significant. However, positive correlations were found between FT4 & FBG and FT4 & HbA1c that were significant at the 0.01 level, as shown in Table 2.

A correlation was also found between T3/FT3 and levels of CHOL, HDLC, and LDLC. The correlations between T3 & CHOL, T3 & HDLC, FT3 & HDLC, and FT3 & LDLC were significant at the 0.05 level while the correlation between T3 & LDLC was

Table 1. Independent samples T-test for comparing the means of two studied groups

Parameters	Mean value (Diabetics)(±SD)	Mean value (Controls)(±SD)	*P*
FBG (mg/dL)	189.6 (± 79.4)	98.6 (± 12.5)	< 0.05*
HBA1C (%)	9.2 (± 2.3)	5.4 (± 0.5)	< 0.05*
T3 (ng/mL)	1.36 (± 0.33)	1.45 (± 0.24)	0.036*
T4 (ng/mL)	84.9 (± 19.9)	85.5 (± 13.8)	0.832
FT3 (pg/mL)	3.12(± 0.49)	3.36(± 0.36)	< 0.05*
FT4 (pg/mL)	15.50(± 2.53)	14.34(± 1.49)	0.001*
TSH (µIU/mL)	3.81 (± 3.92)	2.79 (± 1.83)	0.036*
CHOL (mg/dL)	175.7 (± 46.4)	178.2 (± 25.4)	0.672
HDL (mg/dL)	52.3 (± 12.6)	58.9 (± 11.5)	0.001*
LDL (mg/dL)	114.1 (± 36.1)	114.0 (± 23.76)	0.994

*Significant (P<0.05)

Table 2. Correlation of glycaemic markers with thyroid hormones

Variables	Pearson correlation coefficient	*P*
T3 & FBG	-0.208	0.008*
T3 & HBA1C	-0.179	0.023*
FT3 & FBG	-0.233	0.003*
FT3 & HBA1C	-0.299	<0.01*
T4 & FBG	-0.053	0.500
T4 & HBA1C	-0.022	0.780
FT4 & FBG	0.233	0.003*
FT4 & HBA1C	0.218	0.005*

*Significant (P<0.05)

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significant at the 0.01 level. These were found to be positive, meaning that higher levels of thyroid hormones corresponded to higher levels of circulating lipids, as shown in Table 3.

There was no significant correlation between T4/FT4 and CHOL/HDL/LDL (Table 3). There was also no significant correlation between TSH and any of the above-mentioned markers- FBG, HbA1c, HDL, LDL, or CHOL.

A significant negative correlation of HDL with FBG & HbA1c was found. However, there was no significant correlation between the glycaemic markers and CHOL or LDL. This implies that poor glycaemic control corresponds to lower levels of HDL, as shown in Table 4.

There was no significant correlation between age and the glycaemic markers. However, a strong negative correlation was found between age & T3 and age & FT3, as seen in Table 5.

Discussion

Peripheral deiodination of T4 releases the more potent hormone T3. Hence, circulating levels of total T3 and free T3 are hallmarks for evaluating thyroid function. The biological functions of thyroid hormones are numerous; however, in DM, the most significant of these is glycaemic control. While thyroid hormones are known to increase blood glucose levels, they are also known to increase the uptake of glucose into peripheral tissues, especially muscles (12).

We hypothesise that in DM, due to a complex feedback system between blood glucose levels and various hormones, there is a compensatory decrease in circulating levels of T3 and FT3. Our results show that T4 is not significantly correlated with glycaemic or lipid markers; we think that this may be due to decreased peripheral deiodination of T4.

As a result, while hepatic gluconeogenesis is

Table 3. Correlation of lipid profile with thyroid hormones

Variables	Pearson correlation coefficient	*P*
T3 & CHOL	0.173	0.028*
T3 & HDLC	0.202	0.010*
T3 & LDLC	0.224	0.004*
FT3 & CHOL	0.126	0.111
FT3 & HDLC	0.166	0.035*
FT3 & LDLC	0.179	0.022*
T4 & CHOL	0.089	0.259
T4 & HDLC	0.044	0.575
T4 & LDLC	0.073	0.359
FT4 & CHOL	-0.013	0.865
FT4 & HDLC	-0.131	0.098
FT4 & LDLC	-0.034	0.666

*Significant ($P<0.05$)

Table 4. Correlation of cholesterol with glycaemic markers

Variables	Pearson correlation coefficient	*P*
FBG & CHOL	-0.070	0.379
FBG & HDLC	-0.280	<0.01 *
FBG & LDLC	-0.080	0.311
HbA1c & CHOL	-0.042	0.595
HbA1c & HDLC	-0.244	0.002*
HbA1c & LDLC	-0.050	0.526

*Significant ($P<0.05$)

Table 5. Correlation of some parameters with age

Variables	Pearson correlation coefficient	*P*
Age & FBG	0.131	0.097
Age & HBA1C	0.149	0.059
Age & T3	-0.229	0.003*
Age & FT3	-0.346	<0.01*

*Significant ($P<0.05$)

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decreased, the peripheral uptake of glucose, and therefore its removal from circulation, is also slowed down. This is further supported by the fact that T3 and its deiodination product, T2, have specific binding sites in the mitochondria. This binding is to the source of several pathways which eventually intersect with insulin. As thyroid hormones increase the activity of mitochondria, they release reactive oxygen species (ROS). Insulin is said to have an antioxidative effect and therefore when ROS are released, there is an upregulation of GLUT-4 receptors. Extrapolating this hypothesis, we can say that when levels of thyroid hormones drop in circulation, there is a downregulation of GLUT-4 receptors and development or worsening of insulin resistance (13).

Commenting on lipid profiles, it is well known that the Indian population generally tends to have a lower level of HDL cholesterol. According to a large scale study (6123 subjects) conducted by Guptha et al (14), the prevalence of low HDL levels is much higher (33.6% in men and 52.8% in women) than high LDL levels (16.3% in men & 15.1% in women) or even high CHOL levels (25.1% in men &24.9% in women). This becomes particularly relevant when we consider that dyslipidaemias increase the risk of cardiovascular complications, especially in DM.

Our statistics show that the mean values of LDL and CHOL are not significantly different in diabetics and non-diabetics. Hence, in DM, the impact of thyroid hormones on HDL assumes greater importance than their impact on LDLand CHOL. As LDL is generally easy to control with exercise and drugs like statins and fibric acid derivatives, it is good to note that T3 and FT3 show an incremental effect on HDL levels.

However, it may be noted that literature shows that higher circulating levels of thyroid hormones are correlated with lower levels of LDL and CHOL (15).We attribute this contradiction to various factors like different study designs, laboratory methods and practices, bias in statistical analysis (16), difference in populations such as geographical, climatic, and ethnic, etc.

While it has been well known that subclinical thyroid disorders become more prevalent with older age, in the context of DM, this finding provides insight into a possible explanation as to why achieving adequate glycaemic control becomes increasingly difficult with age. This could imply that poor glycaemic control in older patients may not be singly due to lack of dietary control; diminished function of the thyroid gland due to senescence (17) and lower levels of circulating T3 and FT3 maybe some of the key factors in worsening of insulin resistance in old age. Early detection of thyroid dysfunction and initiation of therapy for the same can improve the treatment outcome of hypoglycaemic drugs (18).

Conclusions

To summarise, our study showed that high-normal circulating levels of T3 and FT3 are correlated with improved glycaemic control (measured by blood glucose and HbA1c) and higher levels of CHOL, LDL, and HDL. We recommended that thyroid profile of diabetic patients, especially those with poor control, should be monitored regularly (annually or biennially). Early detection of thyroid dysfunction and therapy can improve the treatment outcome of hypoglycaemic drugs.

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Conflict of Interest

The authors declare no conflict of interest.

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