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THYROID GLAND RESPONSES TO THERAPEUTIC INTERVENTIONS IN ELDERLY DIABETES TYPE 1 AND TYPE 2 SUBJECTS OF NORTHERN PAKISTAN

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Abstract
A total of 330 study participants with type 1 and type 2 diabetes were involved in the study in a noninterventional setting, they were placed on different therapies for diabetes and thyroid disorders based on clinical protocols. The objective of these treatments was to evaluate their impact on thyroid gland function. Thyroid stimulating hormone (TSH), total thyroxine (T4), free thyroxine (fT4), total triiodothyronine (T3), and free triiodothyronine (fT3) levels were measured to evaluate the thyroid gland's functional status across different therapeutic interventions. It was observed that TSH levels were significantly elevated in subjects treated with insulin alone for type 1 diabetes, as well as in those receiving a combination of insulin and oral antidiabetic drugs for type 2 diabetes. Furthermore, T4 and fT4 levels were significantly reduced in groups with elevated TSH levels, indicating a decrease in thyroxine biosynthesis and subsequent negative feedback response on TSH secretion. Similar patterns were observed in the levels of free T3 (fT3), suggesting a reduction in triiodothyronine biosynthesis. Notably, T3 levels were also lowered in subjects receiving oral antidiabetic drugs alone or in combination with other treatments. The findings highlight the importance of periodic monitoring of thyroid function in type 2 diabetic subjects undergoing oral antidiabetic treatment, as these medications may adversely affect thyroid function and necessitate adjustments in treatment strategies. Overall, the study underscores the need for careful consideration and management of thyroid function in diabetic patients undergoing various therapeutic interventions, to optimize treatment outcomes and minimize potential adverse effects.

Key words: Non interventional study, insulin, oral antidiabetic drug, therapeutic treatments. TSH, T4, fT4, T3, fT3.

Introduction

The leading factors in the physiological homeostasis are the chemical coordinators of which the dominant are the hormones of endocrine glands [1]. The overexpression and under expression of the hormones in the constantly challenging factors maintain the homeostasis [2]. The persistence of the over-expression or otherwise in certain circumstances may cause a sustainable shift in homeostasis to establish a disorder and manifest the disease and it is referred as adaptive homeostasis [3].

Thyroid globally is the most vulnerable among endocrine glands to adaptive homeostasis causing thyroid disorders specifically of iodine deficiency in diet [4]. Iodine Deficiency Disorders (IDD) are a major public health problem worldwide affecting all groups of people of which children and

lactating women are the most vulnerable categories [5]. Almost onethird of the world's population including Pakistan live in areas of iodine deficiency despite major national and international efforts to increase iodine intake, now iodine deficiency is an emerging issue in industrialized countries, previously thought of as iodine-sufficient [6].

Endocrine pancreas responsible for glycemic homeostasis is another gland which in the modern life style of high caloric consumption undergoes adaptive disorderly state of insulin resistance of type 2 diabetes [7]. Endocrine pancreas and thyroid gland disorders are more profound than others and responsible of major health concerns globally [8]. Thyroid disorders and diabetes mellitus often coexist and are closely related. In type 1 and type 2 diabetes, there is a high chance of thyroid dysfunction [9]. Several studies have shown a higher prevalence of thyroid disorders in patients with diabetes mellitus and *vice versa* [10]. There are wide range studies on the relationship where thyroid and its disorders affect the endocrine pancreatic functions, however the effects of normal and disorderly states of endocrine pancreas on thyroid gland activity has comparatively received less attention.

The understanding of endocrine pancreas functional status on thyroid activity is gaining importance with rising epidemic of type 2 diabetes due to obesity. Obesity is a triggering factor for diabetes associated with insulin resistance or the type 2 diabetes [11]. Investigating the complex and mutual relationship between the thyroid axis and adiposity several mechanisms have been identified which affect thyroid function [12]. The thyroid diseases are found to be highly common in T1DM patients as compared to T2DM, and it is considered that every third person suffering from T1DM will ultimately develop dysfunction of thyroid gland[13].

Hyperinsulinemia in metabolic syndrome and type 2 diabetes mellitus is the indirect opportunity to observe this relationship. The hyperinsulinemia stimulate the proliferation of thyroid tissues, enhance the occurrence of thyroid disorders, and induce goiter [9]. Type 2 diabetes in early stages can affect the thyroid tissues by inducing hyperplasia, which increases in size and cause growth of the thyroid gland [14]. Decreased FT3 is strongly correlated with the in type 2 diabetes [15].

In type 1 diabetes and its link with thyroid is established with higher prevalence of thyroid disorders in patients with type 1 diabetes mellitus (T1DM) [16]. Type 1 diabetes is frequently associated with thyroid dysfunction and can raise the probability of Hashimoto's thyroiditis and Graves' disease [9].

Drugs and treatment regimens used to treat diabetes, thyroid disorders, as well as other chronic conditions can affect the function of thyroid glands or blood glucose control in people who have both Type 2 diabetes mellitus and thyroid dysfunctions. There are studies claiming that antidiabetic medications can increase the risk of thyroid cancer [17]. Thyroid function can be affected by diabetes medications, and glycemic control can be altered by antithyroid medications [14]. As a result, using such medications to treat patients with Type 2 diabetes may affect the circulatory levels of thyroid functional hormones and hypothalamuspituitary-thyroid axis activity associated with thyroid function [18]. Treatment with amiodarones including metformin has been linked to a variety of thyroid effects varying from minor metabolic derangement to obvious hypothyroidism [19].

A non-interventional study in diabetics in middle age and elderly subjects receiving their required therapeutic treatments of diabetes and thyroid disorders provides crucial information on the thyroid functional status. Such information may reveal homeostatic adaptability to the extent of altering thyroid function and correcting the therapies for better management. Thus present study had been carried in the elderly diabetic subjects of thyroid challenging northern region of Pakistan on the above objective to enhance the understanding of the health management in elderly subjects in general and specifically to the conditions of a region.

MATERIAL AND METHODS

Sampling of the Study Participants

Different hospitals in the north and center of the Punjab province as representative of northern Pakistan were surveyed preliminarily with the intention to target and select the sample population in accordance with the research work objectives prior the final sampling. The study was non

interventional and nothing was predetermined except synchronized to collect the data and samples while the clinicians were managing and treating the subjects at the health facilities. All these non-interventional procedures were shared with the clinicians of the health facility with approval of each of the clinical facility administration and consent of the participants was sought thus to fulfill the ethical approval requirement.

Grouping of the Sampled Population and Therapeutic Treatments

Grouping of the worked out subjects/patients was not pre-determined because of noninterventional study. The groups were carved out from the data depending on the type of diabetes mellitus (DM), combination of the treatments for the DM and the thyroid disorder. A total of 330 subjects were included in the study with the number of diagnosed subjects with disorder/s was 309, and 21 patients were classified as control group. The data showed that 175 were males and 134 were females in the diagnosed subjects. The subjects other than the normal received the standard therapeutic treatments insulin, oral antidiabetic and thyroid disorders treatments.

Hormones and Glycemia Assaying and Analysis

Blood samples were obtained, processed for sera. The sera was stored at -20 degree centigrade until used for assays. Blood sugar was monitored by health staff with standard Glucometer of Roche Company. Hormones were assayed using Enzyme Linked Immunoassay test kits of Monobind Inc, Lake Forest, CA, USA. These AccuBind ELISA Microwells are of high specificity and accuracy and widely employed for assays and widely used in health diagnoses. Groups data was obtained as mean and standard error of mean and group comparisons were done employing Student T except that in test and one way ANOVA at $P<0.05$.

RESULTS

Thyroid functional hormones including thyroid stimulating hormone (TSH), total thyroxin (tT4), free fraction of thyroxin (fT4), total triiodothyronine (tT3) and free fraction of triiodothyronine (fT3) along blood glucose were determined for their concentrations in the untreated normal and type 1 and type 2 diabetic subjects receiving the therapeutic treatments of insulin alone, oral antidiabetic drug alone and combined treatment of insulin and oral antidiabetic drug while receiving thyroid disorder treatment also with no intervention.

Blood Glucose

Diabetes status on basis of fasting and random non-fasting blood sugar level in different therapeutic treatments is presented in Table 1. The random and fasting blood glucose levels in various treatments establish the diabetic status of the subjects in the study specifically comparing with normal subjects. There is no specific contrast in both type 1 and type 2 diabetes mellitus (T1DM and T2DM) except oral antidiabetic therapy fasting blood sugar level is 18% significantly lower in type 1 compare to diabetic subjects' to type 2 diabetes.

Table 1. Blood sugar mg/dL in the clinically normal and type 1 & type 2 diabetes mellitus subjects with various conventional treatments. All subjects except clinically normal were receiving thyroid disorder treatments. * Significant different $P<0.05$ from each other.

Subjects' Status / Treatment	Fasting Blood Sugar Levels mg/dL Mean ± SEM				Random Blood Sugar Levels mg/dL Mean ± SEM	
	N	Diabetes Type 1	N	Diabetes Type 2	Diabetes Type 1	Diabetes Type 2
Clinically Normal	21	80.71±1.89	21	80.71±1.89	108.19 ± 3.82	108.19 ± 3.82
Oral antidiabetic (Oa) only	17	113.20 ± 9.9*	58	138.88 ± 6.1*	226.00 ± 4.74	208.47 ± 2.47
Insulin (I) only	5	139.35 ± 4.04	17	139.53 ± 1.76	223.29 ± 4.79	216.95 ± 2.32
Combined Oa % I	20	102.30 ± 4.63	69	97.19 ± 1.74	229.35 ± 4.93	219.07 ± 1.88

Thyroid Stimulating Hormone (TSH)

T1DM: The insulin treatment group demonstrated significantly raised level of TSH compared to the rest of the treatments groups (Fig. 1A).

T2DM: The combined treatment of insulin and oral antidiabetic drug significantly elevated the level of TSH compared to the rest of treatments among the respective groups (Fig. 1B).

There is clear contrast in the response of TSH to the specific treatments in T1DM and T2DM.

Total Thyroxin (tT4)

T1DM: The hormone has been observed highly significantly suppressed in the subjects receiving insulin compared to other treatment in the respective groups (Fig.1C).

T2DM: The combined treatment of insulin and oral antidiabetic drug inhibited significantly the hormone compared to other treatments in the respective groups (Fig.1D).

Parallel to the responses of TSH, in case of total thyroxin also the significant responses are in contrast with different treatments in T!DM and T2DM.

Free fraction Thyroxin (fT4)

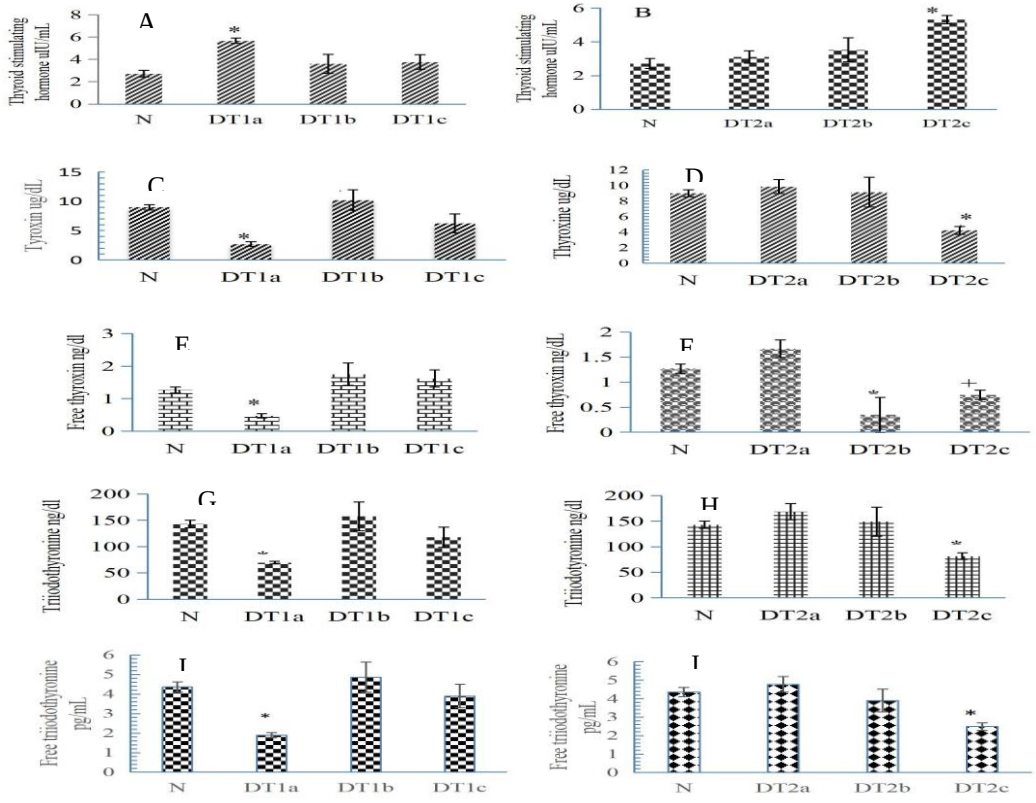
T1DM: Similar to total thyroxin the free thyroxin was observed significantly reduced in concentration with insulin treatment compare to other therapies (Fig. 1E).

T2DM: Both oral antibiotics drug alone and in combination with insulin significantly suppressed fT3 compared to other treatments (Fig. 1F).

The fT4 responses to the therapies are different in T1DM and T2DM.

Total Triiodothyronine (tT3)

T1DM: Insulin treatment showed significant lowered hormone concentration compared to other therapies (Fig. 1G).T2DM: Combined treatment of insulin and oral antidiabetic drug therapies significantly suppressed the hormone (Fig.1H).The hormone also demonstrated variable responses in two types of the diabetes.



Fig, 1. Thyroid functional hormone' concentration mean with standard error of mean in type 1 (DT1) and Type 2 (TD2) diabetic subjects receiving therapeutic treatment of insulin (a), oral

antidiabetic drug (b) and combined treatment of insulin and oral antidiabetid drug (c); N (Normal subjects no treatment); * & +Significantly P=<0.05).

Free Fraction Triiodothyronine (fT3)

T1DM: In this hormone as well the significant effect of reduction in concentration was observed with insulin treatment group (Fig. 1I).

T2DM: The significant response of inhibited release of the hormone with combined treatment of insulin and oral antidiabetic drug occurred in this type of diabetes (Fig. 1J).

The fT3 distinctly responded to treatments in T1DM and T2DM).

DISCUSSION

In the present study thyroid gland functional deviations based on thyroid hormones circulatory levels visualizes that within the therapeutic treatments of type 1 and type 2 diabetes mellitus thyroid gland periodic monitoring will add to better DM management in elderly population specifically in the region like northern Pakistan with environmental challenges of deficient iodine availability to thyroid gland. Varied thyroid functional responses have been found in type 1 and type 2 DM. The present study merited in completion of non-interventional category in which the medical product(s) is (are) prescribed independent to inclusion of the participant in the study; and as part of a therapeutic strategy including diagnostic and monitoring procedures are not decided in advance by a study protocol but are applied according to the current clinical practice [20]. This is suitable approach in less developed regions otherwise because of the expenses almost 90% of biomedical and clinical researches in such regions did not mature to be reported [21]. The above discussion highlight the significance of the present investigation because both of endocrine pancreas and thyroid gland are most vulnerable to adaptive homeostasis and turn out to be the dominant factors in the health scenario of the present times.

The significantly lowering of glycemia in type 1 compare to type 2 DM with oral hypoglycemic therapy is not only the contrasting but also unusual result between the types of DM. The most administered metformin is the first line of an oral hypoglycemic drug for the treatment of type 2 diabetes [22] because of its glucose-lowering effects by reducing hepatic glucose production and enhancing glucose utilization in skeletal muscle and adipose tissue. In the present study such effect has not been expressed. Contrary to it in type 1 metformin has shown glucose lowering effect. It may not be considered as unusual because in type 1 diabetes mellitus the scanty reserves of β cells are highly potentiated by oral hypoglycaemic drugs to produce sufficient endogenous insulin for glucose utilization. These drugs' mechanism of action involves a direct secretory effect on the pancreatic islet beta-cells which by adenosine triphosphate (ATP)-sensitive potassium channels (K+ATP) of the beta-cells play an essential role in the release of insulin [23]. Additionally sulfonylureas a class of the oral antidiabetic drugs lower the serum glucose levels by increasing sensitivity to insulin in peripheral tissues [24]. Thus the current study reveals that employing of oral antidiabetic drugs in type 1 diabetes is useful strategy for blood glucose regulation.

In the patterns of thyroid functional hormones TSH highly significantly increased with insulin treated subjects in type 1 diabetes, however in type 2 diabetes the combined treatment of insulin and oral antidiabetic drug significantly elevated TSH. Pharmacological doses of insulin to the patients of DMT1 is not the replacement of the physiological releases of insulin. Thus pharmacological insulin doses inducing a sort of hyperinsulinemia may be the reason of TSH elevation through the axis of thyroid hormones in negative feedback mechanism pattern as the lowering of circulatory thyroid hormone in negative feedback elevates TSH. In the negative feedback relationship the increase in TSH is the result of lower release of thyroid hormone [25]. It is reported that hyperinsulinemia can also be associated with goiter as well as with thyroid nodules and these are the hypothyroid states [26].

In DMT2 subjects TSH level is significantly greater however in the combined insulin and oral antidiabetic treatments compare to the normal, insulin only and oral antidiabetic treatment only.

Although in each of the group treatment is significantly higher than the normal subjects. It is already well established that DMT2 is characterized of hyperinsulinemia that is elevated level of circulatory insulin. Thus TSH mechanisms are already adapted to the raised insulin levels; therefore additional insulin administration did not affect the hormone significantly in DMT2. The marked increase in TSH in the combined treatment of insulin and oral antidiabetic agent may be considered the overwhelming effect of oral antidiabetic drug as insulin alone has already been found not to affect TSH. In DMT2 also like DMT1 the raised TSH may be the feedback response of decreased secretion of thyroid hormone from thyroid gland. The decreased thyroid hormone in negative feedback elevated TSH in order to overstimulate thyroid gland in order to compensate the decreased secretion of thyroid hormone from the gland. In a study at children Welfare Hospital, Baghdad, Iraq it was reported that thyroid autoimmunity may be associated with poor diabetic control and elevated TSH levels, indicating subclinical hypothyroidism that may affect the diabetic control [27].

The lower level of thyroxin in the insulin treated subjects in T1DM confirms that TSH elevation is due to hypothyroid state of the group. Similarly lower T4 in the combined treatment of oral antidiabetic agent and insulin in T2DM also confirms the TSH elevation in this group in feedback response to significantly reduced thyroxine. The lower T4 generally is the result of reduced biosynthesis of the hormone. In T1DM insulin treatment significantly reduced thyroxin level. In T2DM combined treatment of oral antidiabetic drug and insulin reduced thyroxine however the drug alone did not affect the hormone level. Oral antidiabetic agents are known to cause reduced biosynthesis of hormones in thyroid rendering it hypothyroid. Treatment with amiodarones including metformin has been linked to a variety of thyroid effects varying from minor metabolic derangement to obvious hypothyroidism [19]. This hypothyroid effect of metformin however is not resolving the difference in T2DM subjects where alone oral antidiabetic drug remained ineffective to thyroxin level but in combination with insulin highly significantly reduced the hormone. The feedback response of TSH ascertains the reduced thyroxine secretion from the gland however the cause of reduced thyroxin level selectively in certain treatment is wide open.

Free thyroxine pattern is similar to the total thyroxine pattern both in T1DM and T2DM except in T2DM both oral antidiabetic drug alone and in combination with insulin significantly reduced the free fraction of the hormone. The hypothyroid effect of the drug is well manifested in T2DM in the results of the free fraction of the hormone. Target cells of thyroxine possess proteinases to free thyroxin from its bound protein. The concentration of free T4 is governed by the concentration of total T4 and serum binding capacity [28] and free thyroxine is the biological active part of thyroxine. The pattern of total T3 and fT3 is quite similar to tT4 that is significantly reduced with insulin treatment in T1DM and with combination of the drug and insulin in T2DM. The lowering of tT3 along tT4 provide an evidence that thyroid hormones reduction is the result of hormones' biosynthetic anomaly. Thyroid hormones are released from thyrocytes by endocytosis and proteolytic enzymes cleave of which T4 largely and one quarter of it T3 is released [29]. In increased demand the target tissues contain 5′-iodinase, which can convert T4 into T3 [30]. In the current studies in T2DM the insulin resistance diabetes, free T3 is lowered in combined treatment of the drug and the insulin and in other comparisons there are no significant results. In a contemporary study a higher fT3 was significantly associated with higher fasting glucose and higher fasting and 2-h postload insulin levels that is the characteristic of insulin resistance of T2DM. Further many of these associations between thyroid markers and parameters of glucose metabolism were significant in young and middleaged participants but not in older individuals [31]. The result of present study is in agreement to that as fT3 did not increase in elderly subjects, however unlike to this result it was reduced and that only in combination treatment of oral antidiabetic drug and insulin. The consistent lowering of thyroid hormones and their free fractions suggest that in type 2 DM subjects receiving oral antidiabetic treatment require periodic monitoring of thyroid function for the treatment adjustments because of its adversely affecting thyroid function.

It is assessed that a non-interventional study incur low cost with greater probability of completion and reported. In addition it may provide fine tuning in the health management of the disorders.

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