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THYROID FUNCTIONAL STATUS IN VARYING CONVENTIONAL TREATMENTS OF TYPE 2 DIABETES IN MIDDLE AGE AND ELDERLY POPULATION OF NORTHERN PAKISTAN

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ABSTRACT

Thyroid functional status had been investigated in type 2 diabetic middle age and elderly subjects already receiving the treatments of insulin alone, oral antidiabetic alone and in combination of the both along the same age groups of clinically normal subjects however all not receiving any thyroid related treatment. The functional status of the gland was assessed through assaying of thyroid stimulating hormone, thyroxin, fee fraction of thyroxin, tri iodothyronine, free fraction of tri iodothyronine and reverse tri iodothyronine. In all the diabetic groups on various treatments random non fasting glycemia was well beyond 200 mg/dL. Thyroid stimulating hormones was highly significantly elevated in alone and in combination of insulin of oral antidiabetic treatments compare to the insulin alone treatment and the normal subjects' groups. All the assayed thyroid hormones were highly significantly lowered in diabetic subjects receiving oral antidiabetic alone or in combination with insulin compare to insulin only treatment and the normal subjects' groups. There is strong evidence that oral antidiabetic treatments adversely affect early steps of thyroid hormones' formation which persists without any modulation at the subsequent steps thus lowering all types of thyroid hormones.

Keywords: Type 2 diabetes, oral antidiabetic, insulin, thyroid stimulating hormone, thyroid hormones

INTRODUCTION

The relationship of insulin and thyroid hormones is of high significance in the hormonal homeostasis. The lack of insulin and insulin resistance in hyperinsulinemia represent type 1 and type 2 diabetes mellitus respectively. Epidemic rise in obesity has proportionally resulted in increased risk of insulin resistance and developing type 2 diabetes **[1]**. Insulin and thyroid hormones both antagonistically participate in cellular metabolism thus increase or decrease in any one of these may cause metabolic derangement **[2]**.

Various studies had elaborated the ways insulin axis affect thyroid responses as hypothyroidism is common in people with poorly managed diabetic who are admitted to the hospital **[3]**. In addition, majority of these individuals' thyroid dysfunctions improved once their blood glucose corrected **[4]**. The secretory response of the thyroid gland to significant dosages of TSH reduced in Patients with type 2 diabetes mellitus with poorly managed diabetes, and stringent glycemic management enhanced the response **[5]**. Poor glycemic control blunted or abolished the nocturnal TSH peak with impaired the TSH response to TRH **[6]**. Reduced levels of T3 have been reported in uncontrolled diabetic subjects because of an impairment in peripheral conversion of T4 to T3 that normalized with improvement in glycemic control **[7]**. The amelioration in glycemic control did not restore the impaired nocturnal TSH peak suggesting adaptability in insulin lack or absence cause changes in the central control of TSH **[8]**. Higher levels of circulating insulin associated with insulin resistance have shown a proliferative effect on thyroid tissue resulting in larger thyroid size with increased formation of nodules **[9, 10]**. The relationship of greater incidence of insulin deficient or type 1 diabetes had been reported in patients with Grave's orbitopathy compare to the normal population **[11]**.

More than five decades ago antithyroid effect of oral hypoglycemic or antidiabetic agents were formally investigated and reported **[12]**. These were introduced to enhance insulin release from the depleted beta cells of endocrine pancreas in diabetes mellitus. These were also reported to enhance peripheral uptake of glucose. Sulfonylurea as glibenclamide have been in use as oral antidiabetic drugs however a dimethyl-biguanide or metformin also in practice more than five decades however has proven to be effective antidiabetic drug presently **[13]**. It has been reported a few years ago that metformin treatment decreased serum TSH level in hypothyroid patients which increased again on discontinuation of metformin **[14]**. Additionally significantly increased thyroid

volume and a higher prevalence of incident goiter and nodules in prediabetes and type 2 diabetes mellitus was found that in subjects treated with metformin had smaller thyroid volume and low incidence of formation of goiter and nodules **[15]**.

Pakistan particularly in its western Himalayan region, thyroid diseases particularly on reduced glandular function are more common **[16]**. Various studies have reported the occurrences of thyroid diseases in different regions **[17, 18]**. Numerous studies have shown the strong relationship of type 2 diabetes including the treatments on thyroid function. Thus a study on such relationship is a necessity in the regional perspective. Therefore present study is carried out to assess thyroid functional status in type 2 diabetic subjects which already have been receiving various diabetes treatments however not receiving any thyroid disorder treatment.

MATERIAL AND METHODS

The study was conducted at various health centres and hospitals in Rawalpindi, Lahore and Sargodha regions of Punjab, Pakistan from January 2020 to June 2021. The subjects visiting these health centres were approached at Out Patient Departments after they have consented for collection of data and blood samples. The visiting patients had been examined for their health, screened for the diabetes and its type and the status of the treatments for type 2 diabetes and thyroid disorder. In the screening the particulars of the visiting subjects were collected in routine while those had been under investigations and the necessary clinical treatments. Among the three hundred and fifty documented subjects around two hundred and twenty middle age and elderly subjects included both type 1 and type 2 diabetic subjects receiving various diabetes treatments including many receiving thyroid disorder treatment also. Among the data a handful were found out to be type 2 diabetic receiving insulin alone (n=18), oral antidiabetic alone (n=7) and combination of the both treatments (n=27) in routine without any evident thyroid disorder thus receiving no thyroid treatment. The diabetic status was monitored with fasting and random non fasting glycemia while they kept receiving diabetes treatments.

The middle age and elderly however clinically healthy volunteering subjects (n=21) and the diabetic patients receiving oral antidiabetic, insulin and combination of both were sorted out and sampled for blood that was processed for the serum for assaying thyroid stimulating hormone and thyroid hormones of total thyroxin, free fraction of thyroxin, total tri iodothyronine, free fraction of tri iodothyronine and reverse tri iodothyronine.

Competitive Enzyme Immunoassay Method (ELISA) was employed using the

kits for thyroid stimulating hormone (TSH), total thyroxin (tT4), free fraction of thyroxin (fT4), total tri iodothyronine (tT3), free fraction of tri iodothyronine (fT3) and reverse tri iodothyronine (rT3) for their estimations. The ELISA kits of CTK Biotech, Poway, California, USA (for TSH); Abcam, Cambridge, UK (for tT4, fT4, tT3 & fT3) and Eagle Biosciences, Amherst, USA (for rT3) were used.

The analysis of the data included descriptive statistics, unpaired student t test was applied to get the comparison in-between two groups. One way analysis of variance (ANOVA) was used to compare the means of more than two groups. All the parametric tests were applied by using a software named 'Minitab version 17'.

RESULTS

Thyroid functional status has been assessed in typ2 diabetic middle age and elderly subjects receiving oral antidiabetic, insulin and combined oral antidiabetic and insulin treatments, however without any thyroid disorder treatment along with non-diabetic subjects as controls. Thyroid stimulating hormone, total thyroxin, free fraction of thyroxin, total tri iodothyronine, free fraction of tri iodothyronine and reverse tri iodothyronine were assayed to assess the thyroid status.

Glycemic Status

The glycemic status of the diabetic subjects in different groups while kept receiving varied treatments along the normal subjects was observed in fasting and randomly in unfasted states and the profile is presented in **Figure 1**. Glycemia in all of the groups' subjects was significantly higher compare with fasting normal subjects. The combined oral antidiabetic and insulin treatment group exhibited lowest glycemia compare to alone oral antidiabetic and alone insulin treatments groups. Insulin alone treatment showed lower glycemia than oral antidiabetic alone treatment in fasting. In non-fasting phase randomized blood sugar remained greater than 200mg/dL in all the diabetic groups' with the varied treatments.

Thyroid Stimulating Hormone

The serum level of the hormone was observed highly significantly increased in type 2 diabetic subjects receiving oral antidiabetic alone and in combination with insulin treatments compare to the normal subjects. The hormone's concentration was non-significantly higher in insulin alone treated group however was significantly lower from oral antidiabetic alone and in combination with insulin treatment groups **(Figure 2A)**.

Thyroid Hormones

The pattern of the hormones of thyroxin, free fraction of thyroxin, tri iodothyronine, free fraction of tri iodothyronine and reverse tri iodothyronine (rT3) closely resembled in the type 2 diabetic groups receiving various treatments of the diabetes

along the normal subjects. Every thyroid hormone was observed highly significantly lowered in type 2 diabetic subjects receiving the treatment of oral antidiabetic alone or in combination with insulin. In the groups receiving insulin alone treatment each thyroid hormone was non-significantly reduced compare to the normal group, however was significantly greater than both the groups receiving oral anti-diabetic alone or in combination with insulin **(Figure 2 B-F)**. These results obviously disclose that oral antidiabetic treatment certainly lowers the various thyroid hormones. Insulin alone treatment partly ameliorates thyroid function though the improving effect of insulin is annulled with accompanying treatment of the oral antidiabetic in type 2 diabetic subjects. The decreasing effect in certain treatments appears to be manifested in the early steps of thyroid hormones' synthesis and that pattern remains unaffected at the subsequent biosynthetic steps.

T3 and rT3 Ratio

Thyroxine metabolism into active component of T3 and inactive rT3 depicting their ratio is an important feature of thyroid function. The ratio has been observed to remain unaffected in different treatments in type 2 diabetic and the control groups **(Figure 2G)**.

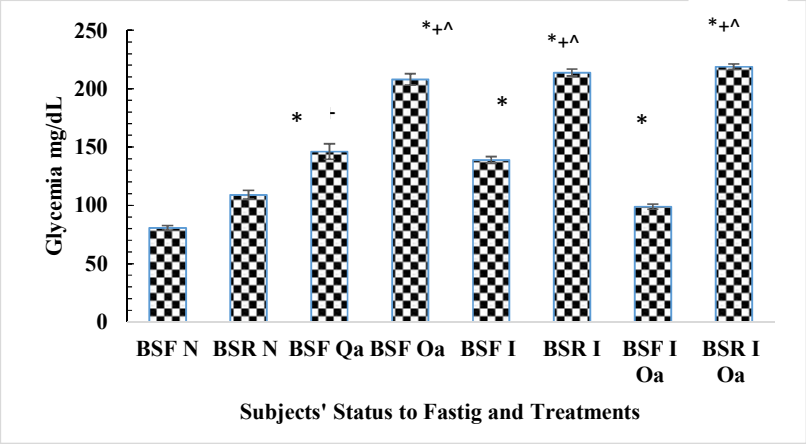

Figure 1: Fasting glycemia (BSF) and random glycemia (R) in clinically normal (N), oral antidiabetic alone (Oa), insulin alone (I), and combined oral antidiabetic &insulin treatedtype 2 subjects. Level of significance P<0.05. *Significantly different from BSF N; + from BSR N and ^ from their respective mean fasting level

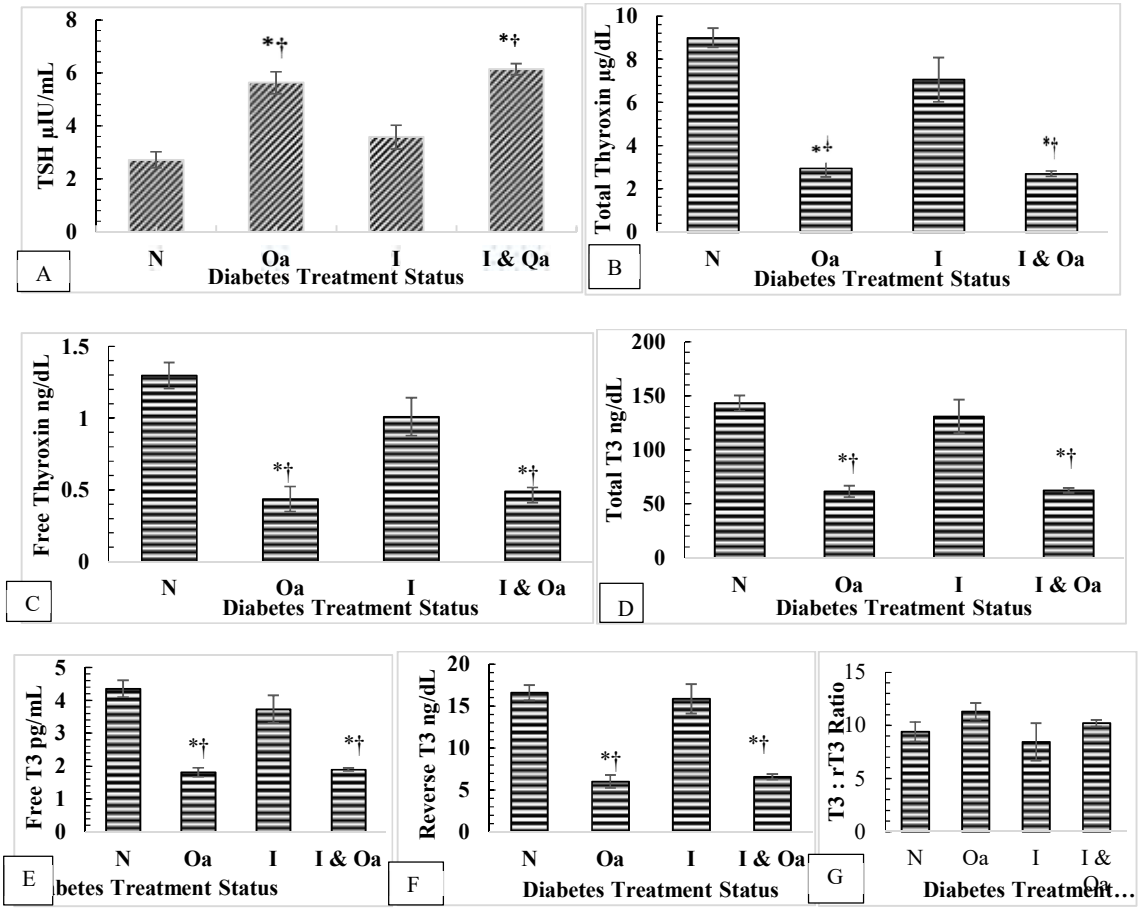

Figure 2: A Serum thyroid stimulating hormone (TSH), B Total thyroxin, C Free thyroxin, D Total tri iodothyronine, E free tri iodothyronine, F Reverse T3 and G T3:rT3 ratio in clinically normal (N) and following oral antidiabetic alone (Oa), insulin alone (I) and combined oral antidiabetic & insulin (I &Oa) treatments in type 2 diabetic subjects. Level of significance P<0.05. *Significantly different from N; † from I

DISCUSSION

It is uncommon opportunity to find a desired situation in human population that otherwise require planned animal model study. The present study of thyroid functional status in type 2 diabetic subjects came across impediment that most of the type 2 diabetic subjects on screening were found to be receiving thyroid disorder treatment. Thyroid disorder treatment in these studied subjects has not been unusual as the northern region of Pakistan is considered significantly higher in thyroid disorders because of the environmental factors. The review accounts of 56 studies those reported goiter/iodine deficiency prevalence in Pakistan and prior to formally adapting the universal iodination programme in 1994 and even after most of the studies had reported more than 50% prevalence of iodine deficiency disorders **[16]**. Similar thyroid disorders situation is reported in pregnant women and children **[17, 18]**. In the analysis of sampling data it was found that there are adequate number of type 2 subjects who had not been

receiving any thyroid disorder treatment along clinically normal subjects. This situation provided the opportunity to assess the thyroid functional status in type 2 diabetic subjects receiving various conventional treatments of the diabetes.

The type 2 diabetic subjects of the study receiving just insulin exhibited non-significant difference from the normal subjects in TSH levels, however highly significantly raised level in oral antidiabetic treatment alone or with insulin. Conversely all the thyroid hormones were observed lower in the subjects on oral antidiabetic alone or in combination with insulin treatments. Thus insulin alone treatment seems to sustain thyroid of type 2 diabetics closer to the normal status as serum TSH and various thyroid hormones did not differ significantly from those in the normal subjects. Insulin role on thyroid function may be assessed by the observation that hypothyroidism is common in poorly managed diabetes **[3]** and their thyroid dysfunction improved once their glycemic level is restored in the normal range **[4]**. This response had been observed in type 1 and also in type 2 diabetes **[5].**

The highly significantly elevated TSH and reduced thyroid hormones levels in the subjects receiving oral antidiabetic treatment with or without insulin clearly demonstrate antithyroid effect of the treatment. Various studies have reported the effect of oral antidiabetic on thyroid as metformin reduced serum levels of thyrotropin depicting improvement in thyroid function in type 2 diabetic patients **[19]**. Similarly effect has been reported in type 2 diabetic women **[20].** In the present study however TSH showed significant increase in oral antidiabetic treated subjects. Additionally all types of the thyroid hormones were highly significantly reduced in antidiabetic drug treated subjects with or without insulin combination. The resultant effect points to interference in an earliest step of the proteinization of iodine in the synthesis of thyroxin; as the subsequent thyroid hormones are the product of thyroxin thus all the subsequent hormones exhibited the same proportion reduction. This mechanism of action is similar to thionamides used in the therapy of thyrotoxicosis of Graves' disease that is inhibiting the synthesis of thyroxin **[21].**

CONCLUSION

It is proposed that in the thyroid vulnerable regions in Pakistan in treatment of type 2 diabetic subjects in general and specifically with oral antidiabetic drugs, thyroid status is required to be monitored periodically for adverse effect on thyroid during the treatment.

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