ORIGINAL ARTICLE

FUNCTIONAL ADAPTATION OF THYROID GLAND IN POSTMENOPAUSAL WOMEN WITH AND WITHOUT DIABETES

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Background: Prevalence of thyroid disorders in general population and in patients suffering from diabetes mellitus is inconsistent in different populations. The combined effect of thyroid dysfunction and diabetes in postmenopausal age may have its specific adaptations from the normal set up. The thyroid profile can provide a link between thyroid and diabetic postmenopausal women of variable ages. The study was designed to compare Thyroid stimulating hormone (TSH), Total thyroxine (TT4), Total triiodothyronine (TT3), Free thyroxine (FT4) and Free triiodothyronine (FT3) in non-diabetic postmenopausal, diabetic postmenopausal and premenopausal non-diabetic females. **Methods:** A total of 78 females from Lahore, Pakistan were recruited for the study and were divided into three groups: diabetic postmenopausal (n=32), non-diabetic postmenopausal (n=33) and premenopausal non-diabetic (n=13). Participant's serum sample was collected after written informed consent and analyzed for the above mentioned thyroid parameters by using ELISA. **Results:** TT4 was significantly greater in diabetic post-menopausal as compared to premenopausal. In diabetic subjects TT3 and FT3 were significantly lower as compared to non-diabetic postmenopausal. Compared to diabetic postmenopausal subjects FT3 level was significantly greater in premenopausal subjects. **Conclusion:** Thyroid gland appears to adapt its function in postmenopausal diabetic and non-diabetics. However, studies on larger population are required for a clear picture.

Keywords: Thyroid profile, premenopausal, postmenopausal, diabetics

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INTRODUCTION

With aging endocrine organs particularly thyroid undergo very important functional changes. Thyroid diseases are common in general population and there is an increased prevalence with increasing age.[1] The main changes that occur in thyroid with age are decreased iodine uptake by the gland, reduced synthesis of free T3 and T4, decreased breakdown of free T4 and increased level of reverse T3, however the concentration of TSH remains normal or shows the tendency towards higher concentration in both genders.[2] The increased risk of thyroid dysfunction with aging is more frequent in females. It is usually missed clinically because symptoms are often similar to changes related to aging.[3]

The effect of menopause on thyroid is related to aging. Menopause can change the expression of thyroid disease especially the autoimmune type. Thyroid may not affect the pathogenesis of the complications related to menopause directly but it is a known fact that hyperthyroidism and hypothyroidism worsen the complications of menopause like atherosclerosis, osteoporosis and cardiac issues.[2] It has been shown that thyroid dysfunction is very common among women over 50 years of age and the symptoms of thyroid disease change with age so it is important to recognize disorders of thyroid in old age. Furthermore, the postmenopausal women are already at high risk to develop various complications and thyroid dysfunction can further exacerbate this risk.[4] A study on Japanese women aged 35 to 59 years showed existence of similarity between menopausal symptoms and symptoms due to thyroid dysfunction which occurred even before menopause. Thus, it is crucial that differentiation between menopausal symptoms and thyroid diseases is required in elderly ladies.[5] Therefore it is highly recommended to screen aged females in climacteric period to rule out subclinical thyroid disease.[6] Prevalence of thyroid disorders in general population and in patients having diabetes mellitus is variable in different populations.[7] The study on diabetic postmenopausal women has not been carried out in our local population. The present research is an endeavor to study the functional state of thyroid in diabetic postmenopausal subjects of varying age.

MATERIAL AND METHODS

This cross-sectional comparative study was partly carried out at Social Security Hospital Lahore and partly at the Centre for Research in Molecular Medicine (CRIMM), The University of Lahore (UOL). The study was approved by the Human Research Ethics Committee of the University of Lahore. A total of 65 postmenopausal female subjects were finally selected by convenience sampling out of hundred and fifty postmenopausal subjects according to required variation of age with and without diabetes. Participants of the study were divided into three groups: diabetic

postmenopausal (n = 32), non-diabetic postmenopausal (n = 33) and premenopausal non-diabetic (n = 13).

The inclusion criteria for all subjects was age 30 years and above and postmenopausal females with and without type 2 diabetes mellitus (T2DM). Non-diabetics were taken as the control subjects for comparison with diabetics. Written, informed consent was taken from each participant, prior to clinical examination and sample collection. Approximately 5 ml blood was collected from each volunteer. The samples were placed immediately in anti-coagulant EDTA tubes between ice-packs and transported to Molecular Biology Laboratory of CRIMM, UOL. Serum samples were collected, labeled, stored and analyzed for the selected biomarkers (serum TSH, TT_4, TT_3, FT_4 and FT_3) by using AccuBind ELISA Micro-wells. Data entry and analysis was done on SPSS version 21.

RESULTS

The mean serum TSH levels were almost in a very close range in non-diabetic premenopausal and diabetic postmenopausal states. In non-diabetic postmenopausal subjects there was a noticeable (8.6%) although insignificant increase in TSH as compared to the non-diabetic premenopausal subjects. There was almost no difference in mean serum TT4 levels between both postmenopausal states. However, mean serum TT4 levels in these two states were greater than premenopausal concentrations. The increase in TT4 in non-diabetics was non-significant however was significantly greater in diabetic post-menopausal states as compared to premenopausal phase (Table 1). In postmenopausal diabetic females mean serum TT_3 was reduced highly significantly as compared to both non-diabetic pre-and postmenopausal states. In the diabetic subjects the fraction of TT3 was 31.8% lower as compared to their respective non-diabetic controls. In non-diabetic premenopausal controls, the TT3 concentration was 8.7% lower compared to non-diabetic postmenopausal subjects. It was significantly (25.3%) lower in postmenopausal diabetics as compared with non-diabetic premenopausal subjects (Table 1).

No difference was observed in mean serum FT_4 levels in diabetic state as compared to non-diabetic and pre-menopause phase. Mean value of FT4 was about 8.0% but not significantly greater in the diabetics as compared to respective non-diabetic subjects. The concentration of FT_3 in the diabetic subjects was 35.9% lower as compared to their respective non-diabetic postmenopausal controls. This difference was statistically significant. In premenopausal non-diabetic controls, the hormone concentration was 2.7±0.4 pg/ml; thus, in comparison to the non-diabetic postmenopausal females the level was 12.4% lower however, non-significant statistically. On the other hand, compared to diabetic postmenopausal subjects the hormone level was 78% greater in premenopausal subjects (Table 1).

Table-1: Pairwise comparison of study variables

Variables	Pairwise comparison					
	Pst Mp N	Pst Mp D	Pst Mp N	Pre Mp N	Pst Mp D	Pre Mp N
TSH µIU/mL	4.1±0.7	3.9±0.4	4.1±0.7	3.7±1.0	3.9±0.4	3.7±1.0
	p = 0.54		p = 0.74		p = 0.99	
TT_4 ug/dL	13.0±0.3	13.1±0.2	13.0±0.3	12.4±0.3	13.1±0.2	12.4±0.3
	p = 0.96		p = 0.62		p = 0.05*	
TT_3 ng/mL	4.8±0.2	3.3±0.2	4.8±0.2	4.4±0.3	3.3±0.2	4.4±0.3
	p = 0.00*		p = 0.83		P = 0.05*	
FT_4 ng/dL	2.0±0.1	2.1±0.1	2.0±0.1	1.8±0.3	2.1±0.1	1.8±0.3
	p = 0.69		p = 0.87		p = 0.87	
FT_3 pg/mL	2.3±0.4	1.5±0.2	2.3±0.4	2.7±0.4	1.5±0.2	2.7±0.4
	p = 0.05*		p = 0.89		p = 0.04*	

*p-value significant (<0.05)
Pst Mp N= postmenopausal non-diabetics
Pst Mp D= postmenopausal diabetic
Pre Mp N= premenopausal non-diabetic subjects

DISCUSSION

It is now strongly realized that the risk of thyroid dysfunction increases with age and is more frequent in females. It is often missed clinically because symptoms often are similar to changes related to aging.[3] Thyroid disease is a common finding in most types of diabetes and is usually associated with old age, particularly in T2DM. An Australian study highlighted the presence of subclinical hypothyroidism (8.6%) in women with T2DM. They however have concluded that in women with T2DM without known thyroid disease; subclinical hypothyroidism was found common but as an incidental finding; thus, routine screening of thyroid function in T2DM is debateable.[8]

In the present study, the females approaching post-menopausal stage naturally, have been assessed for thyroid gland activity. A group of premenopausal subjects was also assessed similarly for comparison to understand postmenopausal adaptations in the background of premenopausal status. In the study population TSH did not exhibit a significant difference in various comparison groups with respect to age. Likewise, in a recent study on aged subjects, apart from effects on T3 and T4 fractions the concentration of TSH has been reported to remain normal or shown the tendency towards higher concentration in both genders[2]. On the contrary, significant changes in TSH concentration have also been reported in a study, concluding that with increasing age, in the absence of autoimmune subclinical hypothyroidism, an age related physiological fall in TSH takes place. However, the researchers did not find any feedback response in terms of effect on total and free thyroxine levels and reported the mechanism to be unknown.[9]

There is a possibility that TSH decrease is due to reasons other than adaptation in aging. This assumption supports the observation of the present study. A study in elderly Jews demonstrated significantly higher median serum TSH concentration, compared with younger controls.[10] It is in line with the present study's observation on TSH. Therefore, present study proposes that TSH concentration in the circulation is not affected significantly in postmenopausal non-diabetic and diabetic subjects.

The results of TT4 in the present study reveal that in diabetic postmenopausal subjects the levels of TT4 are significantly greater than those in premenopausal. Mere non-reproductive aging if been the reason then it also had shown significant difference between non-diabetic postmenopausal and premenopausal groups. Thus, diabetes seems to be more likely cause of greater TT4 than premenopausal status. In diabetes the utilization of thyroxine is probably reduced in non-reproductive phase. The high values of T3, T4 and inappropriate secretion of TSH in old age have been observed along with the signs of decreased sensitivity of pituitary gland to the negative effect of thyroid hormones in women.[11] Free fraction is the expression of TT4, thus the rise of FT4 is the expression of rise in TT4. So, it is assumed that progesterone is the probable factor in the rise of TT4, as observed in the present study.

Total T3 was found almost in the same range in pre-and postmenopausal subjects, however in postmenopausal subjects TT3 was significantly lower in diabetic group compared to non-diabetic group. Therefore, it is quite evident that type2 diabetic state which is expected to be due to insulin resistance lowers the TT3 levels. The circulatory TT3 is the result of deiodination in the thyroid follicle epithelium or in the various target tissues of TT4. There are other studies that have reported the lowering of TT3 in T2DM. The levels of T3 and T4 were reported low significantly and level of TSH was significantly higher in patients having T2DM as compared to healthy individuals without diabetes.[12] There are two possibilities of low TT3 in the present study. One is the inhibition of monodeiodinase converting TT4 to TT3 and the other is the likely metabolism of TT4 to rT3. In both cases deiodination mechanism is the target.

In order to be more certain which metabolism pathways mostly follow in the postmenopausal diabetic subjects, the concentration of rT3 will provide more elaborate information. Nevertheless, the present study demonstrates that TT3 is significantly reduced in diabetic postmenopausal subjects, therefore in these individuals, thyroid activity assessment and the necessary therapy will certainly be useful for their health sustenance. Free fraction of T4 did not exhibit a significant difference in the general population of comparing groups of postmenopausal non-diabetic and diabetic subjects and non-diabetic premenopausal subjects.

In postmenopausal diabetics the concentration of FT3 was significantly lower than the non-diabetic subjects. That is also lower than the premenopausal group. The lowered TT3 and its free fraction as FT3 in the diabetic state of postmenopausal women are directly related. The lowering of FT3 may be the result of lowering of TT3 as specifically in T4 it is supported by investigation data that free fraction is positively correlated to total fraction of the hormone. The other possibility is that the deiodination of FT4 into FT3 is comparatively reduced probably through reduced activity of the relevant monodeiodinase. The possibility of lower FT3 due to markedly lower TT3 seems to be most likely. There are studies from which it may be assessed that FT3 is affected in diabetic postmenopausal subjects than the non-diabetics. Not only the Postmenopausal state affects thyroid, but diabetes is the additional factor added to aging. Furthermore, if diabetes has been due to central obesity in elderly, it further adds to thyroid dysfunction. In a study following the assessment of the numerous parameters it was concluded that prevalence of hypothyroidism is very high in patients with T2DM especially at 45 years of age or above.[13] Thyroid status must be screened in T2DM to prevent the aggravation of clinical course of disease.[14]

CONCLUSION

Thyroid gland appears to adapt its function in postmenopausal diabetics and non-diabetics. These results emphasize the assessment and management of health and disorder of thyroid in aged women. However, larger study population may be assessed for more generalization of results.

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