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ANOMALOUS HIGH OCCURRENCE OF THYROID DISORDERS IN THE FEMALE POPULATION OF KARAK AREA OF KHYBER PAKHTUNKHWA, PAKISTAN

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ABSTRACT

The occurrence of thyroid disorders in the female population has been investigated in the Karak area of Khyber Pakhtunkhwa, Pakistan that had been overlooked due to extreme conservatism in the region. The subjects were sampled randomly in six localities of the district. Circulatory levels of thyrotropin, total and free fractions of thyroxin and triiodothyronine, thyroid peroxidase and thyroid specific immunoglobulin were immunoassayed. The hormonal and related profile of each individual was sorted out on the standard criteria to diagnose the thyroid status. The disorders of hypothyroidism, subclinical hyperthyroidism, mild hyperthyroidism, hyperthyroidism and sick euthyroid were identified in the studied population. A very high incidence of 77% of thyroid disorders with just 23% standard euthyroid subjects are reported form the area. On the inclusion of sick thyroid along euthyroid subjects still 59% of the studied subjects had a kind of the glandular disorder. This is in high contrast to thyroid health in the male population. The factors manifesting such an anomalous thyroid status are being in elaboration.

Keywords: Karak Pakhtunkhwa, female population, thyroid disorders, high occurrence

INTRODUCTION

Endocrine diseases are increasing globally however with greater occurrence in Asia **[1]**. About 0.2% of deaths in Nepal are due to endocrine disorders with the major share of thyroid disorders **[2]** and nearly similar is the scenario in most regions of the world. Thyrotropin (TSH) and thyroid hormones have crucial roles for the regular functioning of physiological systems thus various genetic and environmental factors change the levels of thyrotropin and thyroid hormones resulting in thyroid disorders and TSH holds the status of most important chemical marker of thyroid function **[3]**. Many environmental factors have been reported to affect thyroid function **[4]**. The occurrence of infection, genetic and environmental factors such as lymphocytic infiltrations, thyroid stimulating hormone receptor (TSHR) and different thyroid antigens are the reason of thyroid autoimmune diseases **[5]**.

The greater incidence of thyroid disorders in females is well recognized as one in every eight women during their life time has risk for thyroid disorder. Various surveys have suggested of high incidence of thyrotoxicosis in women comparably very low in men **[6]**. Although the exact reason yet to be established however the cause is attributed to female reproductive hormones also **[7]**. Additionally thyroid diseases in women are confronted with infertility, persistent miscarriage and deprived consequence pregnancy **[8]**.

In Pakistan in general and particularly in its province of Khyber Pakhtunkhwa, being in the western Himalayan region, thyroid diseases particularly on reduced glandular function are more common **[9]**. Various studies have reported the occurrences of thyroid diseases in different regions **[10, 11]**. A little is documented on the gender difference in prevalence of thyroid disorders **[3]** because of conservative status of women remain unnoticed in public health concerns.

The present study is carried out to investigate the status of thyroid disorders in the female population of Karak district of KPK following noticing that occurrence of thyroid disease seems high in female population**.**

MATERIAL AND METHODS

A slight south of the central Khyber Pakhtunkhwa (KPK) on eastern border along the border of the Punjab in Pakistan is the area titled as Karak district. In general it spreads on low mountainous area including of Hindu Kush. In the public health information and research literature reveals that the area is affected with thyroid health issues. The researcher ancestrally belongs to

the area and had been visiting it as resides in other urban area of KPK.

It had been come to know through preliminary survey that Karak area has thyroid related health issues and was revealed that it is significantly observed high in the female population. The concerns of logistics and security specifically were managed and location for the research work chosen. The selected inhabitations in the district Karak thus include Zebichenakhel, Lawagharchenakhel, Upper Lawagharchenakhel, Kamalizarakhel, Kandakhel and Ghundimerankhel. The females of these area culturally and traditionally remain mostly confine to homes and generally exposed to local produced foods, water and environmental factors, thus consume the water and foods produced locally unlike the males which travels to other areas. Through a questionnaire inquiries related to age, weight, and height, sources of water consumption, type and source of food and personal or family history of thyroid diseases were obtained. The female subjects of the chosen areas of district Karak had already been counseled and were pleased to volunteer for blood sampling at the clinical facility titled as 'Basic Health Unit' of the Government of KPK situated in the vicinity of the chosen study areas. The blood sampling of the females was randomly collected at the each location.

Competitive Enzyme Immunoassay Method was employed using the kits for thyrotropin (TSH), total thyroxin (TT4), free fraction of thyroxin (FT4), total triiodothyronine (TT3), free fraction of triiodothyronine (FT3), thyroid peroxidase (TPO) and thyroid linked immunoglobulins (IgG) antibodies were employed for their estimations. The kits were titled AccuBind ELISA Microwells of Monobind Inc. CA, USA. The essential reagents required for an immunoenzymometric assay include antibodies with high affinity and specificity (enzyme conjugated and immobilized) with different and distinct epitope recognition and native antigen are the most important reagents of immunoenzymometric assay. After equilibrium is attained, decantation or aspiration was done to separate bound antibody fraction from the unbound. The enzyme activity in the antibody-bound fraction is directly proportional to the native antigen concentration. A dose response curve was generated or by employing several different serum references of known antigen values.

The diagnostic criteria of thyroid status in the sampled population was based on 'Assessment of Thyroid Function: Towards

an Integrated Laboratory - Clinical Approach' **[12]**. The pattern of the all the hormones assayed in each female subjects was analyzed on the diagnostic criteria to place it in normal or specific thyroid disorder status.

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

In randomly selected six localities of the Karak area female subjects were randomly sampled from each locality from the consenting volunteers. The localities included Zebichenakhel, Lawaghar-chenakhel, Upper Lawagharchenakhel, Kamalizarakhel, Kandakhel and Ghundimerankhel and included 17, 13, 15, 15, 16 and 14 number of female subjects respectively. The functional status of thyroid of each subject on the assessment criteria had been determined and subjects were assorted in six categories of thyroid status **(Table1)**.

Table 1: Thyroid status of the subjects sampled in different localities of the Karak. Zebich: Zebichenakhel, Lawagh: Lawagharchenakhel, Up Law: Upper Lawagharchenakhel, Kamaliz: Kamalizarakhel, Kanda: Kandakhel and Ghundi: Ghundimerankhel

Thyroid Status	Locality						Total		Average Status Prevalence
	Zebich	Lawagh	Up Law	Kamaliz	Kanda	Ghundi	Nos.	%	
Euthyroid	3	6	5	3	3	1	21	23	3.50 ± 0.719
Sick Euthyroid	2	0	2	3	5	4	16	18	2.67 ± 0.715
Hypothyroid	9	4	2	4	4	5	28	32	4.67 ± 0.955
Mild Hyperthyroid	0	0	1	0	0	1	02	02	2.00 ± 0.258
Subclinical Hyperthyroid	2	2	3	2	2	1	12	13	0.34 ± 0.211
Hyperthyroid	1	1	2	4	1	2	11	12	1.83 ± 0.477
All type	17	13	15	16	15	14	90	100	15

Overall Prevalence of Thyroid Status in Sampled Localities of Karak District

Among the total ninety subjects sampled at different six region 21 were euthyroid constituting 23%, 28 comprising 32% were hypothyroid, the sick euthyroid constituted 18% as number was 6 in the whole population. Eleven comprising 12% of the total were hyperthyroid and twelve subjects constituting 13% were of subclinical hyperthyroid status were diagnosed in total sampled subjects. Only two that is approximately 2% exceptional were found to the diagnoses criteria as early or mild hyperthyroid out of the ninety subjects.

The Proportional Thyroid Status in to Sampled Population of Karak District

Inthe total ninety subjects sampled at different six regions mean prevalence of each category of thyroid status was calculated for an overall comparison of the disorders in the sampled area. It was found that euthyroid constituted 3.50 ± 0.72, sick euthyroid disorder 2.67 ± 0.715 and hypothyroid disorder was calculated to be 4.67 ± 0.95 subjects per locality. The prevalence of hypothyroidism has been found significantly greater than sick thyroid and euthyroidism however statistically non-significant. The expression of hyperthyroidism has been 1.83 ± 0.47 subjects per locality and of subclinical hyperthyroid 2.00 ± 0.258 subjects per locality. Early or mild hyperthyroid disorder was diagnosed in one locality only therefore the average was expressed merely 0.34 ± 0.21 subjects per locality. All the categories of the hyperthyroidism were significantly lower than euthyroid category in comparisons **(Figure 1)**.

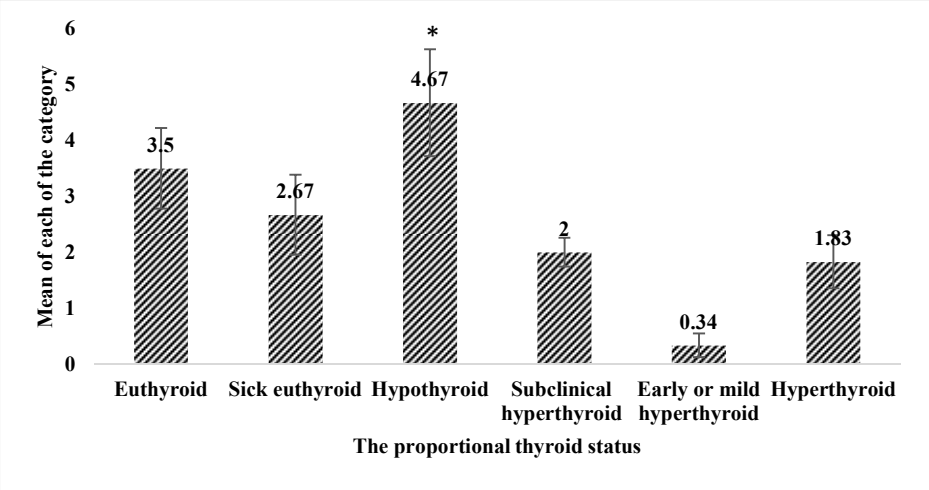

Figure 1: The proportional prevalence of thyroid status in the sampled female population. Mean ± SEM; *P =< 0.05 statistically significant from all other thyroid states except euthyroid

Thyroid Status in Major Functional Categories in Sampled Population of the Karak Area

The sampled population was assessed in three major functional states of thyroid. The categories of euthyroid and sick euthyroid were merged; similarly the all the three categories of hyperthyroid were merged to observe the pattern in the euthyroid, hypothyroid and hyperthyroid states. Thirty seven euthyroid subjects among the total of ninety constituted 41% of the total. There were 28 subjects of hypothyroidism representing the 31% of the population and 25 cases of hyperthyroid category sharing 28% of the total. It is evident that the studied population had demonstrated markedly higher incidence of hypothyroidism, similarly

hyperthyroid disorders are also significantly greater. Thus almost 60% of sampled population had demonstrated thyroid disorders compared to the proportion of euthyroid subjects. The thyroid disorders are almost 50% greater than the normal or euthyroid subjects of the sampled population **(Table 2)**.

Thyroid Function Hormones in Various Thyroid States at Karak Area

In hypothyroid subjects mean circulatory thyrotropin was significantly greater in concentration from euthyroid, sick euthyroid, and various types of hyperthyroid states. In various hyperthyroid states thyrotropin was observed suppressed significantly. Total thyroxin had been exhibited significantly lower in hypothyroid and elevated in all hyperthyroid state compared to the euthyroid subjects. Free fraction of thyroxin almost replicated the pattern of total thyroxin. Total triiodothyronine did not demonstrate significant differences among the various states of euthyroid, hypothyroid and hyperthyroid states. Conversely the free fraction of triiodothyronine revealed significant variations almost in all the thyroid states with suppressed in hypothyroid and sick thyroid states and elevated in hyperthyroid states. The free fraction of T3 even showed significant differences in the various states of hyperthyroid subjects. Thyroid peroxidase had been significantly suppressed in hypothyroid subjects and elevated significantly in hypothyroid states. Thyroglobulin linked immunoglobulins had been specifically observed significantly increased in hyperthyroid subjects **(Table 3 and 4)**.

Table 2: The functional status of major thyroid categories

Sr. No.	Distribution of Thyroid Status in Major Categories	No of Subjects	% Prevalence
1	Euthyroid	37	41
2	Hypothyroid	28	31
3	Hyperthyroid	25	28
Total Subject		90	100

Table 3: Thyroid function hormones level in various thyroid status

Thyroid Status	n	TSH µlU/ml	TT4 µg/dl	FT4 ng/dL	TT3 ng/mL	FT3 pg/ml)	TPOIU/mL	IgG IU/mL
Euthyroid	21	1.251 ±0.180	8.209 ±0.157	1.145 ±0.063	1.114 ±0.059	3.178 ±0.103	18.49±3.63	17.46±1.41
Sick euthyroid	16	1.855±0.342	8.151±0.388	1.061±0.077	1.187±0.052	2.196±0.131	102.2±27.7	39.4±14.9
Hypothyroid	28	5.430±0.306	6.075±0.195	0.629±0.067	1.189±0.053	2.083±0.047	178.8±39.5	232.6±89.5
Hyperthyroid	11	0.305±0.037	11.164±0.508	2.000±0.212	1.443±0.196	5.056±0.258	237.3±34.0	521±355
Subclinical Hyperthyroid	12	0.241±0.034	8.299±0.329	1.222±0.110	1.377±0.152	3.899±0.336	72.17±9.43	35.67±8.86

Table. 4: Multiple comparison among all five categories, significant and non-significant resultsin female'spopulation.P=< 0.05 statistically significant in comparisons.Upper head arrow is the increased and lower head arrow is the decreased level in comparisons

Multiple comparison among all 5 categories	TSH (µlU/ml)	TT4 (µg/dl)	FT4 (ng/dl)	TT3 (ng/mL)	FT3 (pg/ml)	TPO(IU/mL)	IgG(IU/mL)
Hypothyroid - Euthyroid	P <0,000↑	P <0.000↓	P <0.000↓	P =0.956	P <0.000↓	P <0.001↑	P =0.542
Hyperthyroid -Euthyroid	P = 0.198	P <0.000↑	P <0.000↑	P =0.135	P <0.000	P <0.000↑	P <0.050↑
Subclinical hyperthyroid-Euthyroid	P = 0.128	P = 1.000	P = 0.983	P = 0.303	P = 0.023↑	P = 0.762	P = 1.000
Sick Euthyroid -Euthyroid	P = 0.526	P = 1.000	P = 0.969	P = 0.977	P< 0.000↓	P = 0.295	P = 1.000
Hyperthyroid-Hypothyroid	P <0.000↓	P <0.000↑	P <0.000↑	P =0.322	P <0.000↑	P =0.738	P =0.457
Subclinical hyperthyroid--Hypothyroid	P <0.000↓	P <0.000↑	P <0.000↑	P =0.595	P <0.000↑	P =0.156	P =0.765
Sick Euthyroid-Hypothyroid	P <0.000↓	P <0.000↑	P =0.007↓	P =1.000	P =0.981	P =0.371	P =0.668
Subclinical hyperthyroid-hyperthyroid	P = 1.000	P <0.000↓	P <0.000↓	P =0.993	P <0.000↓	P = 1.034	P = 1.126
Sick Euthyroid-Hyperthyroid	P = 0.009↑	P <0.000↓	P <0.000↓	P =0.409	P <0.000↓	P = 0.087↓	P =0.077↓
Sick Euthyroid-Subclinical hyperthyroid	P <0.004↑	P=0.998	P=0.826	P=0.672	P <0.000↓	P =0.977	P =1.000

DISCUSSION

Khyber Pakhtunkhwa is a susceptible region to thyroid health being hilly area probably deficient in iodine content. The study deemed necessary because thyroid is a crucial body and hardly any physiological function escapes the participation of the gland as thyroid hormones regulate metabolic processes not only in regulating metabolism in adults but also crucial for normal growth and development **[13, 14]**. Karak district mostly comprise scattered habitations in small scale populations. Socially is an extreme conservative area, the females remain confined to their houses and dependent upon mostly on local food resources. Adult males mostly work in other may be far areas. It had been grasped that females of the area suffer from neck gland disorders. The classical definitions of thyroid disorders of hypothyroidism and hyperthyroidism reflect this concept when referring to inadequate - either reduced or exaggerated - supply and response to thyroid hormones **[15, 16]**. Pathophysiological conditions or diseases in thyroid may arise at various levels including deficiencies of hormone supply, alterations of control or resistance to cellular responses to the hormones **[17]**. Alteration in the normal thyroid gland activity may have far reaching adverse effects even affecting the subsequent generation. In a Scotland study between 1998-2001 to assess the relationship between

mild maternal thyroid dysfunction at delivery of infants born ≤34 w and neurodevelopment at 5.5 yr. Maternal serum levels and McCarthy scores were employed for cognitive index of the children and gradual decrements had been observed in general cognitive index, verbal subscale, and the perceptual performance subscale with increment in maternal TSH as higher TSH level reveals for reduced thyroid hormones availability **[18]**. Thus female population susceptible to thyroid disorder require immediate attention as maternal thyroid disorders likely to affect next generation causing anomaly during pregnancy and infancy.

The clinical presentation of thyroid disease is highly variable and often non-specific therefore diagnosis of thyroid dysfunction is predominantly assessed biochemically. Thus complex inverse association between the pituitary derived thyrotropin and the thyroid hormones specifically free thyroxin and free tri-iodothyronine renders TSH the more sensitive marker of thyroid status **[19]**. Hypothyroidism is defined as TSH concentrations above the reference range and FT4 levels below the reference range along subclinical hypothyroidism is defined as TSH levels above the reference range, but FT4 levels within the population reference range **[20]**. Likewise, the reverse hormone pattern is applied in the definition of overt (low TSH, high FT4) and subclinical hyperthyroidism (low TSH, normal FT4).

In the present study, the area has been studied on the standard investigation criteria by assessing the hormones and related compounds to identify the types of thyroid disorders in the female population. A marked greater incidence of thyroid disorders in the female population has been found much more than reported in several studies. In the present study 77% of the studied female population possessed one or other type of thyroid disorder including the sick euthyroid. Euthyroid including sick euthyroid along it still constituted 41% and the remaining 59% exhibited the glandular diseases based on thyroid disorder. In the disorderly part of the population hypothyroidism is slightly greater than hyperthyroidism, however insignificant.

Hypothyroidism results from lower availability of iodine the crucial component in the synthesis of thyroid hormones or may be iodine is prevented for the uptake by thyroid gland **[21]**. Certain compound in soil, water and foods termed as goitrogens prevent iodine in the synthesis of thyroid hormones **[22]**. Hyperthyroidism may result from availability of iodine to goiter carrying subjects, a sudden increase in iodine intake in

an iodine-deficient population may induce thyroid autoimmunity **[23]**. In the females steroids of pregnancy elevate thyroid activity **[24]** thus may be contributory in mild and subclinical hyperthyroidism. Very high incidence of thyroid disorders is reported in the studied Karak, the causes are being elaborated or require further investigations on the matter.

CONCLUSION

Globally the different regions in general and hilly sub regions are more unpredictable regarding the occurrences and types of thyroid disorders. Karak area of KPK, Pakistan have demonstrated unusual very high prevalence of thyroid disorders in the female population. The reasons of high prevalence in the studied area are being in elaboration.The study specifically provoke that thyroid status of each population must be worked out for the public health concerns.

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