ORIGINAL RESEARCH

Estimation of serum prolactin levels in hypothyroid patients

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ABSTRACT
The thyroid dysfunction, which is quite prevalent in the population, affects many organs including male and female gonads. Hypothyroidism refers to a state that results in a deficiency of thyroid-hormones, including hypothalamic or pituitary disease and generalized tissue resistance to thyroid hormones. Thyroid-releasing hormone(TRH) can cause a rise in serum prolactin levels in the patients of hypothyroidism. The aim of the present study was to determine the correlation between the levels of Serum Prolactin and Thyroid Dysfunction.**Materials and Methods:** The present study was conducted on 100 newly lab. diagnosed and confirmed cases of hypothyroidism based on the lab. thyroid profile values and 50 healthy age and gender-matched controls. The levels of Serum T3, Serum T4, Serum TSH and Serum Prolactin were estimated in both the study group and in the control group.**Results:** The mean values of serum TSHlevels in the study group and in thecontrolgroup were 14.45±12.96µIU/ml and 1.27±1.05µIU/ml respectively (Normal value of TSH = 0.25-5.00 µIU/ml). The mean value of serum prolactin in the study group and in thecontrol group were 42.70±16.26ng/ml and 14.76±5.09ng/ml respectively (Normal value of Prolactin = 3.0-25 ng/ml). The levels of Serum Prolactin and TSH were increased in the study group as compared to the control group and statistically it was highly significant (p value <0.001). A positive correlation was found between the Serum TSH and Prolactin levels in the hypothyroid patients.**Conclusion:** In our study it was found that hypothyroidism leads to hyperprolactinemia, which further cause ovulatory dysfunction and consequently it leads to Infertility.

Keywords: Serum T3 (Triiodothyronine),T4 (Thyroxine), TSH (Thyroid-Stimulating Hormone) and PRL (Prolactin), ELISA (Enzyme Linked Immunosorbent assay), HPT (Hypothalamic-pituitary- thyroid axis), HPO (Hypothalamic-Pituitary Ovarian- axis), TRH (Thyrotropin Releasing Hormone)

INTRODUCTION
A worldwide reproductive problem that affects both men and women is infertility.[1]India's prevalence rate has increased from 22.4% to 30.7%.[2]The hormone known as "prolactin" is secreted by the pituitary gland and stimulates lactation. The hypothalamus secretes prolactin inhibitor factor, which inhibits the release of prolactin. Prolactin secretion is increased by other factors such as dopamine antagonist, thyroid releasing hormone (TRH), and vasoactive inhibitory peptide (VIP).[3]TRH, in addition to enhancing TSH it also causes a surge in the prolactin levels.[4] Elevated prolactin levels in non-pregnant women interfere with normal hormone production, including progesterone and oestrogen.[3]It has been well acknowledged that thyroid dysfunction dramatically affects the likelihood of conception. It is well recognised that thyroid disorder lowers the chance of becoming pregnant.[5] Several factors, including hypothyroidism, can affect fertility. Increased prolactin levels, luteal phase defects, anovulatory cycles, and a cascade of other hormonal issues, including low sex hormone binding globulin (SHBG), estrogen dominance, and progesterone deficiency, can result from it.Hypothyroidism may also be present in some of the women who have galactorrhoea and hyperprolactinemia. This disease is characterized by low serum levels of thyroxine and decreased negative feedback on the hypothalmo-pituitary axis. The resulting increased secretion of thyrotropin releasing hormone stimulates thyrotrophs and lactotrophs, thereby increasing the levels of both SerumTSH and Prolactin (PRL)Hypothyroidism and hyperprolactinemia are found to be closely

interrelated. In hypothyroidism the decreased feedback of thyroid hormone on the hypothalamus results in elevated thyrotropin releasing hormone (TRH) levels. TRH then binds to the lactotrophs and it further stimulates the release of Prolactinsecretion.[6] However, although a common regulatory mechanism is involved, the sensitivity of pituitary thyrotrophs and lactotrophs differs from common stimulatory and inhibitory substances.[7] The stimulatory effect of TRH is possibly through changes in the number of TRH receptors on lactotrophs as well as alterations in dopaminergic neurotransmitter system.[8] TRH also functions to cause the release of thyroid stimulating hormone (TSH) from the pituitary which is involved in the regulation of the thyroid hormones Triiodothyronine (T3) and Tetraiodothyronine (T4).[9] Furthermore, the elimination of prolactin from systemic circulation is comprised, which leads to increased prolactin concentrations.[10] The role of TRH is releasing of TSH from the anterior pituitary gland is well known but its role in the stimulation of prolactin secretion from the anterior pituitary is still disputed.[11]The present study was conducted to determine the levels of serum prolactin in newly diagnosed hypothyroid patients to find its correlation with the thyroid stimulating hormone (TSH).

MATERIALS & METHODS

The present hospital based analytical study was conducted in the Department of Biochemistry, Government Medical College and Rajindra Hospital Patiala. The study group consisted of 100 newly diagnosed cases on the basis of biochemistry lab. results (TSH $>4.2\mu$IU/ml) and 50 healthy age and gender matched individuals constitute the control group.

This study was initiated after obtaining clearance from institutional ethic committee. Informed written consent was taken from all subjects (Case and controls) in vernacular language.

INCLUSION CRITERIA

Newly detected cases of hypothyroidism on the basis of biochemistry clinical lab. with TSH levels $>4.2\mu$IU/ml, were enrolled in the study group and predominantly in the age group of 20-65 years.

EXCLUSION CRITERIA

The patients with the history of hyperprolactinemia, pregnant women, lactating mothers, chronic renal disease and the patients on antidepressant, antipsychotics and on hormonal therapy were excluded.

METHODS

Serum T3 and T4 levels were estimated by competitive ELISA while Serum TSH and Prolactin levels were estimated by Sandwich ELISA Method.

SAMPLE COLLECTION

A 5 ml of blood was collected from the antecubital vein into red top and grey top vacutainers under aseptic conditions. The blood was allowed to clot and sample was put in centrifuge machine at 2200-2500 rpm for 5-10 minutes for separation of serum. Serum was stored in aliquots at 2-8°C for 5 days and at (-20°C) for up to one month under all aseptic conditions.

STATISTICAL ANALYSIS

The data collected was carried out by using statistical package for the social sciences [SPSS] Version 23.0. Results were expressed as Mean±SD. The statistical significance of difference between the various groups were determined by using the student's test; $p<0.001$ was considered to be significant.

RESULTS

Table 1: Comparison of Age wise distribution between study group and control group

Age (Years)	Study group		Control group		Totals
	N	%	N	%	
20-30	23	23.0	8	16.0	31
31 – 40	40	40.0	21	42.0	61
41 – 50	35	35.0	21	42.0	56
51-65	2	2.0	-	-	2
Total	100	100.0	50	100.0	150

Table 1 shows that the age wise distribution in the study group and in the control group. It is seen from the table that majority of the number of patients were in age group 31-40 years i.e 40% in the study group and 42% in the control group**.**

Table-2 Comparison of Serum T3, T4, TSH and Prolactin Levels between study group and control group.

Parameters	Study group(N=100)	Control group(N=50)	P value
T3 (ng/ml)	0.91±0.30	0.85±0.22	0.204
T4 (µg/dl)	6.08±1.60	5.96±1.57	0.663
TSH (µIU/ml)	14.45±12.96	1.27±1.05	<0.001
Prolactin (ng/ml)	42.70±16.26	14.76±5.09	<0.001

Table 2 shows that the Mean±SD of serum T3 levels were 0.91±0.30 ng/ml in the study group and 0.85±0.22 ng/ml in the control group. There was no significant difference between study group and control group (p value is 0.204). The Mean±SD of Serum T4 levels were 6.08±1.60µg/dl in the study

group and 5.96±1.57µg/dl in the control group. There was no significant difference between study group and control group (p value is 0.663)/ The Mean±SD of Serum TSH levels were 14.45±12.96µIU/ml in the study group and1.27±1.05µIU/ml in the control group. There was highly significant difference between the study group and the control group (p value is <0.001). The mean± SD of Serum Prolactin levels were 42.70±16.26 ng/ml in the study group and 14.76±5.09 ng/ml in the control group. There was highly significant difference between the study group and the control group (p value is <0.001).

Table 3 Pearson's correlation of Serum T3, T4 and TSH with Prolactin.

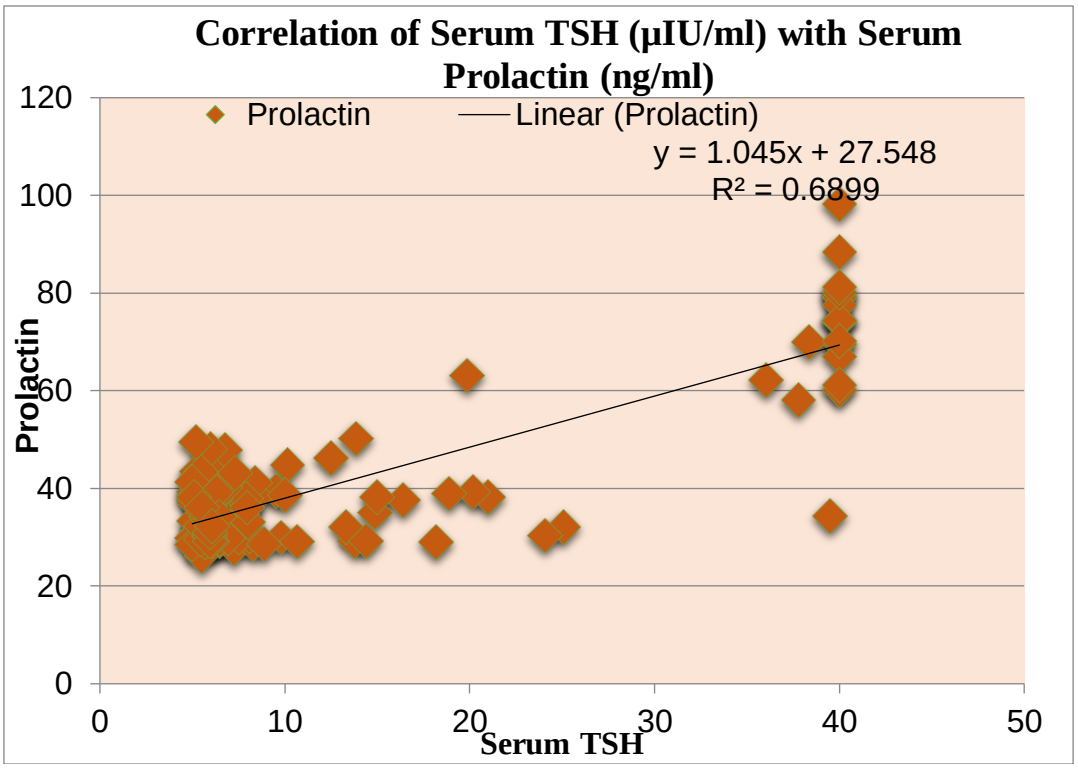
Hormone	R value	P value
Prolactin Vs T3	-0.131	0.195
Prolactin Vs T4	-0.239	0.118
Prolactin Vs TSH	0.829	<0.001

In the table 3 the Pearson's correlation coefficient was calculated for Serum T3, T4, TSH with Prolactin. On analysing the values, there were no correlation on Serum T3(r value -0.131 and p value 0.195) and serum T4 (r value-0.239 and p value 0.118) with serum prolactin levels. There was a positive correlation between Serum TSH levels and Serum Prolactin levels (r value is 0.829 and p value is < 0.001).

Line of regression

$Y=1.0453_X +27.548$

From this graph, it is evident that the coefficient of correlation between Serum TSH and Serum Prolactin is 0.829. This indicates that there is a positive correlation between Serum TSH levels and Serum Prolactin levels and statistically it is highly significant (p<0.001).



DISCUSSION

Thyroid dysfunction and alterations of prolactin levels have been reported as the cause of female infertility.[12] In the present study hypothyroidism was predominantly found in the age group of 20-65 years. In hypothyroidism, prolactin (PRL) suppresses the synthesis and release of gonadotrophins, while higher levels of thyrotropin-releasing hormone (TRH) stimulate the secretion of thyroid stimulating hormone (TSH). A number of investigations have also verified irregular menstrual cycles in cases of overt hypothyroidism.[13]The connection between the infertility and hypothyroidism also has been well established.[14]Hyperprolactinemia is a metabolic disorder most usually linked to infertility. Prolactin can affect the ovaries and result in infertility by altering ovarian progesterone release and estrogen synthesis.[15]High prolactin levels may prevent women from producing adequate progesterone during the luteal phase, which comes after ovulation, even if they

ovulate regularly. The implantation of an embryo in the uterine lining may be hampered by insufficient progesterone, which is produced during ovulation.[16] Hyperprolactinemia resulting from long-standing primary hypothyroidism has been implicated in the ovulatory dysfunction.[17]Infertile females who have hypothyroidism and hyperprolactinemia should get treatment forhypothyroidismfirst and then keep their TSH levels below the recommended levels. There isevidence from both the clinical and experimental investigations that the hypothalamic-pituitary-ovarian (HPO) axis and the hypothalamic-pituitary-thyroid (HPT) axis are closely related to each other. [18] The distribution and activity of Thyroid Stimulating Hormone Receptors (TSH R) and the thyroid hormone receptors (TR) $\alpha 1$, $\alpha 2$ and $\beta 1$ in the human ovarian tissues and in the granulosa cells were studied using Immunohistochemistry, QuantitativePCR and Immunoassay. A Strong Immunostaining ofTSH R, TR$\alpha 1$ and TR$\beta 1$ was observed in the ovarian surface epithelium.[19]The aim of the present study was to shows a significant ($P<0.001$) increase in levels of Serum Prolactin in the study group as compared to the control group.

Valvekar U et al (2016)[20]they determined that the Mean±SD of Serum Prolactin levels in the study group was 44.9±9ng/ml and 25.01±18.4ng/ml in the control group respectively.According toShrif. A et al (2014)[21] studied that the Mean± SD of Serum Prolactin levels in the study group was 40.73±37.07 ng/ml and 8.13±3.66 ng/ml in the control group.Fupare S et al (2015)[22]studied that the Mean±SD of Serum Prolactin levels in the study group was 77±9 ng/ml and 29.7 ±2.01 ng/ml in the control group respectively .In the present study the Mean±SD of Serum Prolactin levels in the study group was 42.70±16.26 ng/ml and the control group was 14.76±5.09 ng/ml and (P value < 0.001). Thus, the findings in the present study regarding the serum levels of prolactin in study group and in thecontrolgroup were consistent with the previous studies conducted by various authors. In hypothyroidism there is increase in the Serum TSH and Serum Prolactin levels and these alterations are mainly produced by the high levels of TRH which is induced by the decreased negative feedback of thyroid hormones at the hypothalamic-pituitary level.[21]

A negative correlation was found between the Serum T3 & Serum Prolactin levels in the hypothyroid patients ($r = -0.131$, $P= 0.195$) and also negative correlation was found between SerumT4 and Prolactin levels in hypothyroid patients ($r = -0.239$, $P = 0.118$). A significant positive correlation was found between Serum TSH and PRL levels ($r =0.829$, $P<0.001$) in the hypothyroid patients. The findings of present study are consistent with the previous studies done by Nath C et al (2015) [23] theystudied that the Mean ±SD of Serum prolactin levels were 14.33±10.71ng/ml and TSH levels were 4.22 ±3.42µIU/ml and Gupta M.K et al (2016)[24] studied that the Mean±SD of Serum Prolactin levels were 20.01±2.04 ng/ml and the Mean±SD of Serum TSH levels were 11.12±0.79µIU/ml in their study groups.

CONCLUSION

Our present study showed that due to hypothyroidism there is increased secretion of Prolactin (Hyperprolactinemia) which cause ovulatory dysfunction which consequently leads to Infertility. So, in the Infertility Profile, the Serum TSH levels and the Serum Prolactin levels need to be estimated in the screening for infertility.

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