Original research papers

Alteration of sex hormone and semen parameters in adult males with subclinical hypothyroidism

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Aim: To investigate the correlation between subclinical hypothyroidism (SCH) with serum testosterone levels and semen parameters (sperm count, total motility and morphology) in men seeking medical care for sexual dysfunction and infertility.
Study design: Cross-sectional study.
Place and Duration of Study: Department of Endocrinology, Gauhati Medical College and hospital, Guwahati, India. Study done from November 2015 to December 2016.
Methodology: The patients in study were grouped into two groups: Group I – Men with subclinical hypothyroidism (n=35) and group II – Euthyroid males serving as controls (n=27). The medical history, clinical examination, semen analysis, total thyroxin(T4), total triiodothyronine(T3), thyroid-stimulating hormone(TSH), Leutinising Hormone (LH), Follicular stimulating hormone (FSH), Total testosterone (T) and prolactin (PRL) were obtained. Patients with diabetes mellitus, hypertension, chronic diseases, any testicular or pituitary diseases and prior chemo-radiotherapy were excluded from study.
Results: The ages of the patients ranged between 24 and 42 years with mean age 31.57 years. The cases had significantly lower levels of mean serum total testosterone and free T4 and higher serum prolactin levels compared to controls (P< .01). Linear regression analysis showed TSH levels independently associated with low testosterone levels. Also men with subclinical hypothyroidism had lower total sperm motility with preserved sperm count and morphology.
Conclusion: We found that SCH is associated with reduction in testosterone levels and total sperm motility. Our study data conclude that SCH may be a contributing factor for hypoandrogenemia and sexual dysfunction in men.

Keywords: Subclinical hypothyroidism; testosterone; sperm count; total sperm motility.

1. INTRODUCTION

Male reproductive function is orchestrated by the hypothalamo-hypophyseal testicular axis. In addition it has been seen that thyroid hormones exerts a modulatory effect on this axis. Thus thyroid hormones seem to play a major role in male sexual and spermatogenic function. Primary hypothyroidism has been associated with low levels of both total and free testosterone in men [1]. The worldwide prevalence of subclinical hypothyroidism is found to be between 4 and 10% [2, 3]. The prevalence of subclinical hypothyroidism in india is about 9.4%. In women, the prevalence was higher (11.4%), when compared with men (6.2%) [4]. But links between subclinical hypothyroidism and male sexual dysfunction and infertility are less evident. Till date there has been no concrete study that has showcased this relationship.

Our study aims to investigate the association between subclinical hypothyroidism with total testosterone levels and semen parameters (sperm count, total motility and morphology) in men seeking medical care for sexual dysfunction and infertility in tertiary care centre.

2. MATERIAL AND METHODS

The study is a cross sectional study done in males of age between 20-45 years, attending Endocrinology department of Gauhati Medical College and Hospital, Assam, India from November 2015 to December 2016 for sexual dysfunction or infertility. The patients in the study were grouped into two: Group I - Men who were subclinical hypothyroidism (n=35) and group II- Men who were normal euthyroid controls (n=27). The most common sexual dysfunction among the subclinical hypothyroid males was erectile dysfunction (26 out of 35) and premature ejaculation (9 out of 35). On the other hand all men among the euthyroid control had presented with only premature ejaculation as the sexual dysfunction. Patients with diabetes mellitus, hypertension, any chronic disease, testicular or pituitary disorder and prior chemo radiotherapy were excluded from study. Patient who fulfilled the study criteria underwent a detailed medical history and clinical examination. Serum samples were collected for free thyroxine (FT4), total triiodothyronine (T3), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicular stimulating hormone (FSH), total testosterone (T) and prolactin (PRL) estimation. Blood samples were collected in the morning after subjects had fasted for at least 8 hours. The samples were immediately centrifuged and the samples were aliquoted into 2-ml tubes .The serum was stored at –80 ℃ until assayed. Hormonal assay was done by enzyme-enhanced chemiluminescent analyzer (IMMULITE 1000). Single semen analysis was also done in pathology department of our medical college with fresh samples collected within 30 minutes of ejaculation. World Health Organization 2010 reference values for human semen characteristics were considered in the study [5]. The study was performed according to the guidelines of the Ethics Committee of our institute with informed consent. Statistical analysis was performed by the use of SAS 9.3. Pearson correlation between TSH levels and LH, FSH, PRL, total testosterone levels and semen parameters were estimated. Linear regression model analysis was used to find independent association between TSH and total testosterone levels .Multiple regression analysis model was used to find the simultaneous effect of thyroid hormones (TSH, Free T4 and Total T3) on the serum total testosterone levels. Statistical significance was set at the 0.05 level. No mention of measuring testicular volume using USG.

.3. Results

3.1 Baseline Characteristics

Table 1 shows the baseline characteristics of the cases and control. Table is not well formed also value till 2 decimal are to be used .Write mean values with their standard deviation values.

Characteristics	Case	Control	*P* value

	(n=35)	(n=27)	
Age(years)	31.5714286	35.5925926	0.0037
Body mass index (kg/m$^{2)}$	24.1357143	24.6518519	0.1054
Testicular volume (ml)	20.8571429	18.5185185	0.0104
TSH (mIU/L)	9.0989143	2.3629630	<.0001
Total Testosterone (ng /dl)	414.2265714	683.2000000	0.0003
Prolactin (ng /ml)	16.2294286	10.7777778	<.0001
LH (mIU/mL)	4.4051429	3.9307407	0.0403
FSH (mIU/mL)	4.7020000	4.6385185	0.215
Sperm count (million per ml)	50.8000000	52.4444444	0.7606
Semen volume (ml)	3.1657143	2.8703704	0.3125
Total sperm motility (in %)	53.1428571	82.8148148	<.0001
Duration of symptoms(years)	4.9714286	3.0740741	0.0014
Free T4 (ng /dl)	1.1731429	1.3237037	<.0001
Total T3 (nmol/L)	1.9234286	1.8400000	0.1835

As seen in table 1, the ages of the patients ranged between 24 and 42 years with mean age 31.57 years (SD ± 5.2). There were no differences between subclinical hypothyroid cases and euthyroid control in terms of mean BMI, mean FSH, mean sperm count, mean semen volume and total T3. However, the cases had significant lower level of mean serum total testosterone levels (414.22 ± 225.48 in cases vs. 683.20 ± 328.29 in controls) and free T4 (1.17 ± 0.14 in cases vs. in 1.32 ± 0.07 controls) but a higher level of serum prolactin (16.22 ± 4.70 in cases vs. in 10.77 ± 2.48 controls) in comparison to control group. LH levels were also significantly different between the two groups (4.40 ± 0.87 in cases vs. 3.93 ± 0.89 controls). Among the semen parameters, the cases had a remarkable lower total sperm motility compared to controls groups (53.14 ± 25.83 in cases vs. 82.81± 16.83 in controls).

Figure1 (A-D) shows the bar diagram comparing the mean values of various hormones (TSH, Prolactin, LH and testosterone) Figures are not properly made ; how can be range of TSH , prolactin and testosterone can be from 0-9 etc.Also the Y axis will always from 0 , do make changes in the fig 2

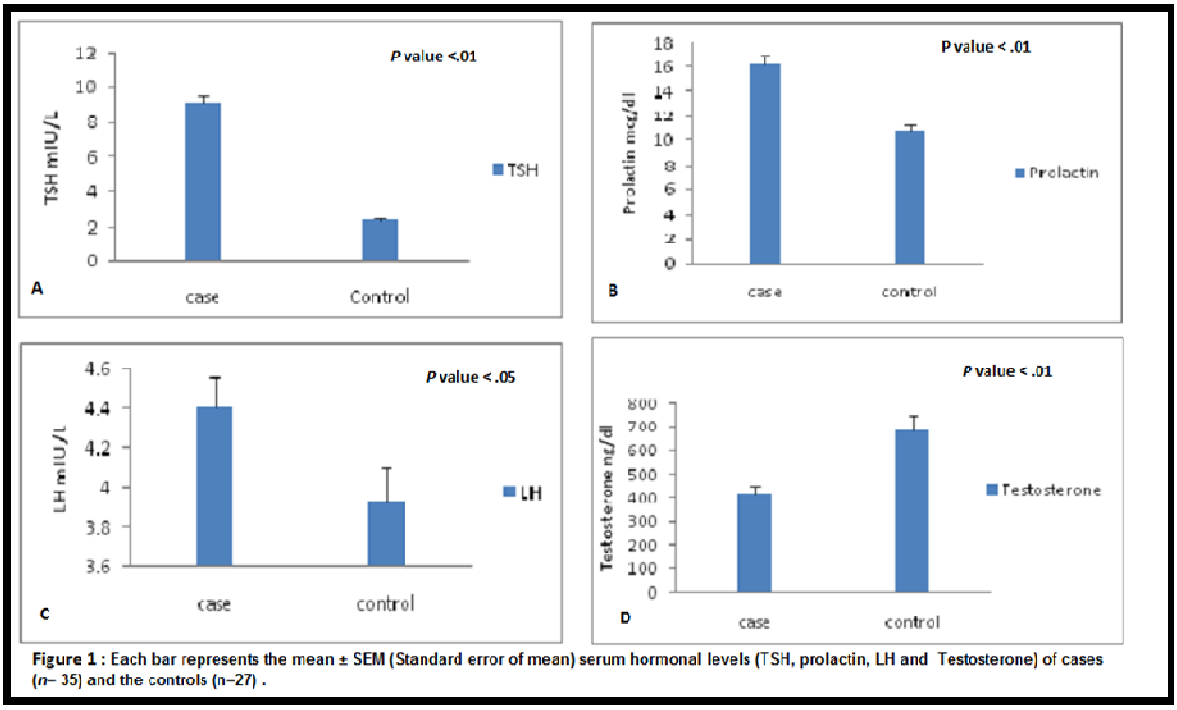

Figure 1 : Each bar represents the mean ± SEM (Standard error of mean) serum hormonal levels (TSH, prolactin, LH and Testosterone) of cases (*n*– 35) and the controls (n–27) .

Figure 2 (E&F) shows the bar diagram comparing the mean values semen parameters among the cases and control groups. Sperm morphology was normal in both the cases and control group as per the Kruger's criteria.

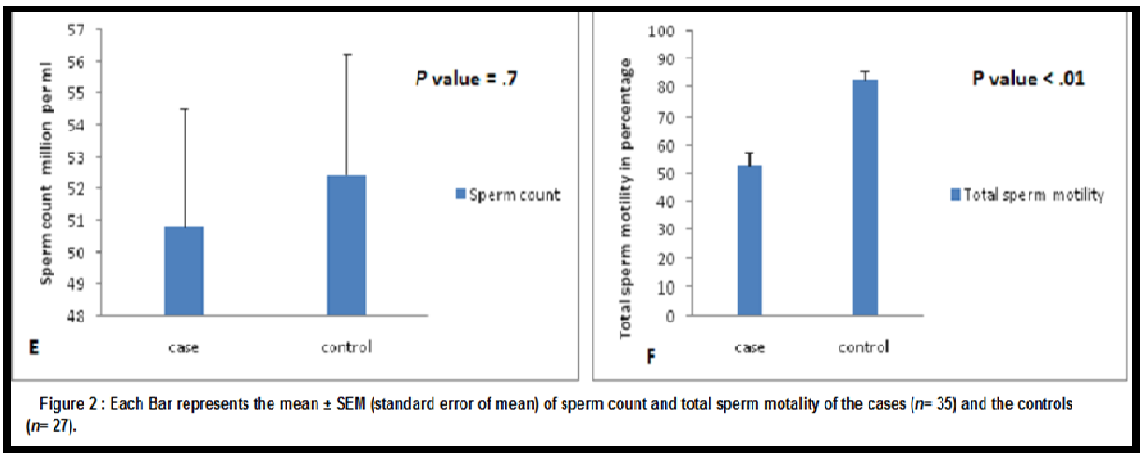

Figure 2 : Each Bar represents the mean ± SEM (standard error of mean) of sperm count and total sperm motality of the cases (*n*= 35) and the controls (*n*= 27).

3.2 *Correlations between TSH and other hormones and semen parameters*

Among the subclinical hypothyroid patients, a significant negative correlation was observed between serum TSH and total testosterone levels (r = -0.75, *P* < .01). Negative correlation was also found between total testosterone levels and serum prolactin (r = -0.69, *P* < .01). Figure 3 (G&H) demonstrates these relationship. Similarly a negative correlation was also seen among the cases between serum TSH and total sperm motility (r = -0.73, *P* < .01). No correlations were found between TSH levels and FSH, LH or sperm count.

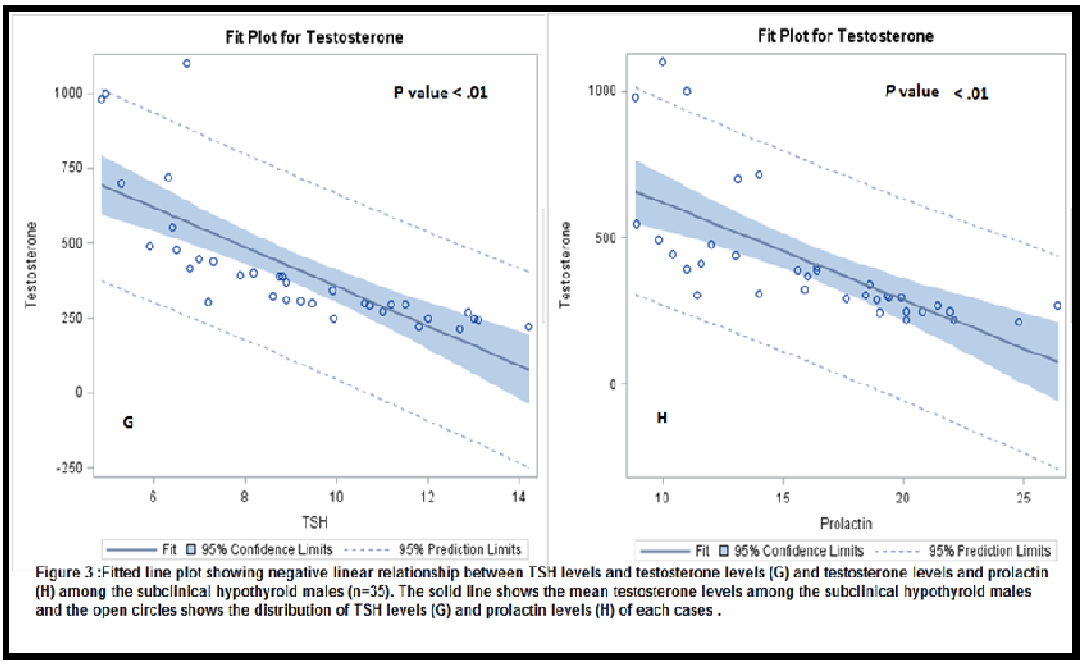

Figure 3 :Fitted line plot showing negative linear relationship between TSH levels and testosterone levels (G) and testosterone levels and prolactin (H) among the subclinical hypothyroid males (n=35). The solid line shows the mean testosterone levels among the subclinical hypothyroid males and the open circles shows the distribution of TSH levels (G) and prolactin levels (H) of each cases .

3.3 *Correlations between testosterone and Free T4 and total T3*

A significant positive correlation was found between total testosterone levels and free T4 and Total T3 levels (r = 0.54, *P* < .01; r = 0.65, *P* < .01). Figure 4 (I&J) demonstrate this relationship.

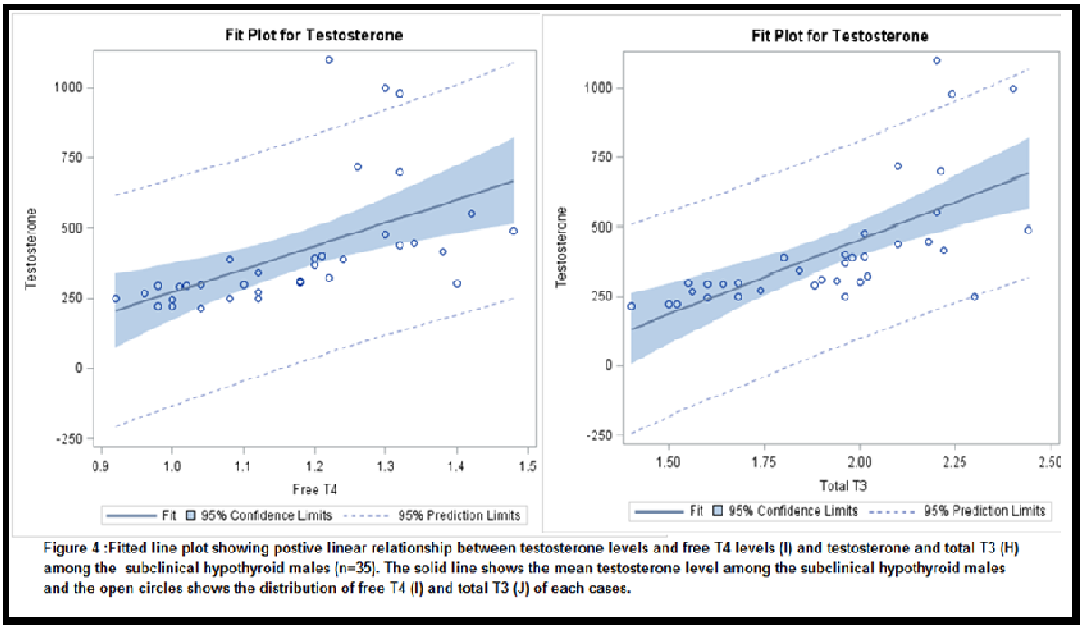

Figure 4 :Fitted line plot showing postive linear relationship between testosterone levels and free T4 levels (I) and testosterone and total T3 (H) among the subclinical hypothyroid males (n=35). The solid line shows the mean testosterone level among the subclinical hypothyroid males and the open circles shows the distribution of free T4 (I) and total T3 (J) of each cases.

Linear regression model analysis showed significant association between TSH and total testosterone levels (P < .01) .Multiple regression model analysis was done to assess the simultaneous effect of thyroid hormones (TSH, Free T4, total T3) on serum testosterone. The model showed TSH and free T4 contributed significantly to low total testosterone level. Table 2 shows multiple regression analysis.

Table 2: Multiple regression analysis showing the relationship between serum testosterone and thyroid hormones.

Hormones	B – coefficient	P Value
TSH	-100.41507	0.0001
Free T4	-920.19167	0.0122
Total T3	147.03873	0.3160

4. DISCUSSION

In the current study we found a significant reduction in serum total testosterone levels in subclinical hypothyroid males compared to euthyroid control. It was also seen that subclinical hypothyroid patients the free T4 levels were significantly lower compared to the control group. The levels if T3 is dependent on the availability of T4 hormone. We could find a positive correlation between total testosterone levels and total T3 concentration (r = 0.65, P < .01) among the subclinical hypothyroid males. This significant correlation explains the role of total T3 in the production of testosterone. The role of T3 hormone in

testosterone synthesis has been demonstrated earlier in Leydig cells of rat and goat [6, 7]. These finding supports the modulatory effects of thyroid hormones in maintaining the normal testosterone levels and male sexual function. However, it has to be understood that serum T3 concentration in subclinically hypothyroid cases was along the lower side but within the normal reference range in this study. Secondly linear regression model analysis showed a significant independent association between TSH and total testosterone levels among subclinical hypothyroid males. The probable explanation lies in the fact that thyroid-stimulating hormone receptors have also been demonstrated in human testis [8]. It is postulated by some authors that TSH may have a cardinal role in regulating testosterone synthesis in leydig cells. However, till date there is no concrete evidence supporting the above. It has to be understood that a negative relationship was found between TSH levels and total testosterone levels. Multiple regression model analysis was done and showed the effects of TSH and thyroid hormones together in generation of testosterone in males. The analysis showed that TSH (beta coefficient: - 100.4) along with thyroid hormones simultaneously has a significant role in testosterone production.

The rise of LH levels seen in subclinical hypothyroid males has been a significant finding compared to the euthyroid control. We postulate that this may be due to loss of feedback mechanism by low levels of testosterone. It should be understood that LH or FSH feedbacks are under the control of free testosterone levels. Our study has been based on total testosterone and hence further confirmation is needed. Moreover the rise of LH and FSH levels in overt hypothyroidism itself is controversial [9,10]. We also found a significant elevation of serum prolactin levels among the subclinical hypothyroid patients. This findings was similar to study done by Kumar et al (2006) [11]. Thought multiple mechanism have been explained as the cause of hypoandrogenemia in elevated levels of prolactin, the degree of hyperprolactinemia required to cause low levels of testosterone has been a consistent finding with overt hypothyroids males. The mechanisms illustrated in overt hypothyroid males include suppression of 17 alphahydroxylase (a key enzyme in conversions of progesterone to testosterone in Leydig cells) [12] and decreasing the binding affinity of LH to its receptors (seen on a murine tumour cell line, MA-10 cells) [13] by high concentration of prolactin. In our study not only a higher levels of serum prolactin were found among the subclinical hypothyroid males but also a significant negative correlation found between total testosterone and serum prolactin levels, ($r = -0.69$, $P < .01$) which probably explains that elevated prolactin as the cause of low levels of total testosterone among the cases. Moreover Kumar et al (2006) in his study has demonstrated the reduced availability of progesterone (precursor for the synthesis of testosterone) in subclinical hypothyroid males. Summating all the above data we may conclude that hyperprolactinemia in subclinical hypothyroid males may lead to hypoandrogenemia a picture similar to overt hypothyroidism.

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Finally we also learned the relationship between subclinical hypothyroidism and semen parameters. Earlier studies have shown that subclinical hypothyroidism had no impact on semen parameter [14]. The

Add some more studies in reference 14

only semen parameter which was affected in our study was the total motility without affecting sperm count and morphology. TSH levels correlated with sperm total motility (r = -0.73, *P* < .01). In overt hypothyroidism it has seen that low levels of thyroid hormone may affect forward progressive motility. Mechanism postulated is that thyroid hormones stimulate cellular oxygen consumption [15] and increases mitochondrial number over the middle and tail piece of sperm [16] and thus promoting sperm motility. This probably is a major drawback in our study as we were unable to sub classify the types of motility defects (progressive motility, non-progressive motility or immotile sperms) among the subclinical hypothyroid males due to limited data. Thought motility defects have been demonstrated among hypothyroid men in earlier studies, motility defects among subclinical hypothyroid males have to be reconsidered. Moreover the mean total motility among the subclinical hypothyroid males fell into a mean value of 53%, which was within the lower reference as per the World Health Organization reference values for human semen characteristics [5] .The small sample size among the cases and control may be another drawback in the study. We also couldn't estimate free testosterone levels among the patients which may be needed to explain the rising levels of gonadotropin levels among the subclinical hypothyroid males.

Add the strength of the study

5. CONCLUSION

In conclusion from our study it was seen that subclinical hypothyroidism may lead to low levels of total testosterone levels. Spectrum of male sexual dysfunction may be a presentation of subclinical hypothyroidism. Till now there is no consensus to treat subclinical hypothyroidism in male. Further studies may be needed to confirm the need for supplementing thyroid hormones to this class of patients. The genesis of infertility in subclinical hypothyroid males remains a domain of interest. Thought the study has concluded the effects of subclinical hypothyroidism on total sperm motility more studies may be required to confirm this findings.

CONSENT (WHERE EVER APPLICABLE)

We declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal."

ETHICAL APPROVAL

We declare that we have obtained all necessary ethical approval from our Institutional ethical Committee.

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APPENDIX