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RESEARCH ARTICLE

A comparative study of sensory-motor coordination, executive function, and testosterone levels in hypothyroid and euthyroid males

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ABSTRACT

Background: Hypothyroidism is an endocrine disorder that is seen much more commonly in females than in males. This could perhaps be due to factors that confer protection against the development of hypothyroidism in males. The male sex hormone testosterone would have protective action on the different systems, probably due to a mechanism of action which is complementary. **Aims and Objective:** To investigate the association between serum testosterone level, audiovisual reaction time, and working memory score in newly diagnosed hypothyroid and euthyroid men. **Materials and Methods:** This was a comparative study. 15 newly diagnosed hypothyroid males between 18 and 45 years of age, recruited from the Endocrinology Department of MS Ramaiah Medical College Hospital, Bangalore, and 15 euthyroid males were assessed for audiovisual reaction time, working memory, serum testosterone, T4, and serum thyroid hormones (TSH). **Results:** Independent *t*-test between hypothyroid and euthyroid groups revealed that there was statistically significant difference in group mean audio-visual reaction time, working memory, serum T4, and TSH levels ($P < 0.05$). **Conclusion:** Hypothyroid patients had longer audiovisual reaction time and the working memory scores were reduced. The serum T4 level was lower and serum TSH level was higher, but the serum testosterone level was not significantly different compared to euthyroid subjects.

KEY WORDS: Reaction Time; Working Memory; n-back Task; Thyroxine; Testosterone

INTRODUCTION

Hypothyroidism is a common endocrine disorder observed to have increased incidence in the recent past. Studies have revealed that its prevalence is higher in females than in males.[1] The reasons for this gender disparity in the prevalence of hypothyroidism are as yet unclear and therefore remain an open-ended question in endocrinology research. The comparatively high prevalence rate in females makes it reasonable to explore the possibility that there may exist some factor that confers protection against its overt manifestation in males. The male sex hormone – testosterone – may have physiological effects similar to or complementary to that of the thyroid hormone – thyroxine – on the various systems of the body. This is particularly true in regards to the central nervous system (CNS), as is evident from the similar symptomatic manifestations in cases of deficiency of either of the hormones. For instance, in the case of thyroid deficiency disorders, the cognitive manifestations most frequently encountered are a constant feeling of tiredness, reduced alertness, poor concentration, and difficulty at memory recall. These are the same symptoms

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that clinically characterize conditions pertaining to the deficiency of testosterone, such as are seen in andropause onset in mid-adult life. However, there are no studies done as yet, to the best of our knowledge, that help delineate the close functional ties between thyroxine and testosterone in the context of their effects on cognition. Since thyroxine is known to have direct effects on the activity of the CNS, its function is likely to be compromised in any patient with hypothyroidism, regardless of their gender. However, when taking into consideration the fact that hypothyroidism is relatively less common in males and more common in females, and the fact that serum testosterone levels are much higher in males than in females, it is reasonable to suppose that the normal levels of circulating testosterone in males could play a supplementary functional role in the situation that thyroxine hormone is deficient. This could explain the lower prevalence rate of hypothyroidism in males as a direct consequence of the masking influence of testosterone, and thus, it's going undetected during clinical evaluation. It is thus, reasonable to explore the possibility that there may exist some or even a variety of factors that confer gender-based protection against the development of hypothyroidism in males.

The two aspects of CNS function that were considered in our study for evaluation are sensory-motor coordination and executive functions. The sensory-motor function was assessed by means of visual-auditory response latency and the executive function component assessed was short-term working memory. It is known that in the condition of thyroxine hormone deficiency, both these faculties are affected as indicated by the parameters used to measure them. However, it is reasonable to propose that testosterone could functionally compensate at least partially, for thyroxine deficiency in male hypothyroid. Response latency may be defined as the time taken to react to a particular stimulus, which may be delivered in any sensory modality, i.e., visual, auditory, or tactile. It may be equivalently defined as the time interval between the delivery of a sensory stimulus and the occurrence of a motor response.[2] Reaction time is, therefore, a measure of sensory-motor coordination as well as internal processing speed in the brain of a sensory stimulus and the occurrence of a motor response.[3,4] The shorter the reaction time, the better is the sensory-motor coordination. Several studies have demonstrated that in hypothyroid individuals the response latency is markedly longer than in euthyroid individuals.[3,5] This objectively underscores the problem of attentional deficit commonly associated with hypothyroidism, wherein the individual has difficulty in directing and sustaining his or her attention on a particular stimulus for long periods of time.

The executive function of the brain assessed in our study was short-term working memory. By virtue of this cognitive faculty, sensory data can be accommodated in conscious awareness for a very short duration of time. This temporary housing of information in the mind allows for its manipulation toward some useful end. For instance, when totaling the price of groceries while shopping or when trying to hold on to a telephone number or a person's name in memory for the first time, it is the working memory faculty that is operating. In hypothyroidism, both of the overt and subclinical kind, studies using neuroimaging technology have shown that there are deficits in the working memory faculty.[6-8] These studies have attributed the memory deficit to be due to the effects of the lack of thyroid hormones on a specific neural substrate in the brain called the hippocampus. Thyroid hormone replacement therapy has been shown to be effective in improving the working memory of patients with hypothyroidism.[9,10]

There are numerous ways to objectively assess the working memory, either in the visual modality or in the auditory modality or in both visual and auditory modalities. In our study, the n-back visual task is used to assess working memory. It is a validated construct for assessing working memory.[11] In this computer-based task, a series of picture frames are presented in a random sequence to a comfortably seated subject. The objective is to respond to a picture frame with a mouse click if it has repeated again after "n" intervening frames in the sequence of presentation. With increasing magnitudes of "n", otherwise referred to as the "load", the burden on the working memory increases and performance as measured by the percentage of the number of correct responses during the task declines.

The primary aim of this proposed study was to investigate the sensory-motor coordination and working memory of a group of newly diagnosed hypothyroid males and to compare their performance to a group of age, education, and anthropometrically matched euthyroid males. The possible protective role of testosterone on cognition in the hypothyroid group was also explored. The sensory-motor coordination and working memory faculties were measured using simple reaction time and n-back task, respectively.

MATERIALS AND METHODS

Calculation of Sample Size

The sample size of the present study was based on a previous work by Shah and Nahar.[5] The minimum sample size required for the present study was estimated to be 15 in each of the euthyroid and hypothyroid groups by taking the effect size of 1.33, an ∝-error of 5%, and a power of 90%.

Study Design, Participants, and General Procedure

This was a comparative study which was granted approval by the Scientific and Ethics Committee of MS Ramaiah Medical College. It consisted of 15 newly diagnosed, right-handed, hypothyroid males between the ages of 18 and 45 years,

recruited from the Endocrinology Outpatient Department of MS Ramaiah Medical College Hospital, Bangalore. The control group consisted of 15 right-handed, anthropometrically and age-matched healthy, euthyroid males. The subjects in each group had normal vision and hearing. Subjects on regular medication, disturbed sleep, neurological deficits, and testicular abnormalities were excluded from the study. Informed written consent was obtained from the participants after explaining the study protocol. They were then assessed for visual-auditory response latency and working memory. Early morning fasting blood samples (5 ml) were collected for assay of serum testosterone, serum T4, and serum thyroid hormones (TSH) using chemiluminescence technique. The normal ranges for serum T4, TSH, and testosterone levels by this biochemical assay technique for the given age group of males are 59–135 nmol/L, 0.5–4.3 μIU/ml, and 1.88–8.82 ng/ml, respectively.

Assessment of visual and auditory reaction time was done using an indigenously designed portable response analyzer device, with a least count of 1/1000 second and powered by two rechargeable AA batteries. Auditory and visual cues consisted of clicks and a flash of green light, respectively. Subjects were first familiarized to the equipment with a practice session. The least of three successive recordings was taken as the reaction time.[3]

Assessment of visual working memory was done using the n-back task. In this computer-based test, a randomized series of picture frames were presented on a screen, one at a time in close succession. The subjects were instructed to respond with a mouse click as quickly and accurately as possible, on a picture if it had appeared 'n' frames earlier. For instance, in a 2-back test, the subject is required to click on a particular picture if it had previously appeared two frames before. Hence, if a picture of a fish is followed by a picture of a cake, which is then followed by a picture of a fish again, the subject is required to click on this last frame because it had appeared two frames before. The subjects were tested for 2-back, 3-back, and 4-back loads. Subjects were first familiarized to the task with a practice session. Each trial began with a center fixation cross on the screen for 500 ms, followed by the picture stimulus in that location for 500 ms, and followed by a 2000 ms interstimulus interval. The number of correct responses made was automatically calculated (in percentage) at the end of each trial. The average score for three successive trials at a given task load was taken as the working memory score.

Statistical Analysis

All the quantitative parameters were summarized using descriptive statistics such as mean and standard deviation. All qualitative parameters were expressed in terms of proportion. Independent sample *t*-test was used to compare the means of reaction times and memory scores in both the euthyroid and hypothyroid groups. Correlation between reaction time (or memory score) and serum testosterone and TSH, T4 was analyzed using Pearson's correlational analysis.

RESULTS

Data were subjected to non-parametric, normality testing using Kolmogorov–Smirnov's test and normal distribution was observed for each parameter. Two-tailed independent *t*-test for equality of means reveals that both euthyroid and hypothyroid groups are age and anthropometrically matched [Table 1].

The group means for visual-auditory reaction time, working memory scores (n-back task performance), and serum hormone assays were compared using independent *t*-test [Tables 2-4]. $P < 0.05$ was taken to be statistically significant. There was statistically significant difference in group mean audiovisual reaction times, working memory scores, serum T4, and TSH levels. However, the difference for serum testosterone levels was not statistically significant.

Pearson's correlational analysis was used to do a bivariate analysis between serum testosterone, thyroid hormones (T4, TSH), n-back task scores, and visual-auditory reaction times. The Pearson's coefficient computed between these parameters for both groups, with each parameter taken pairwise revealed that there is no significant correlation ($P > 0.05$) between: (i) Serum testosterone and visual-auditory reaction times, (ii) serum testosterone and n-back task scores, (iii) serum TSH and visual-auditory reaction times, (iv) serum TSH and

Table 1: Comparison of different parameters between groups

Parameter	Group 1	Group 2	Difference of means	*P*
Age (years)	28.40±5.902	30.13±7.492	−1.733	0.487
Height (cm)	173.60±8.407	170.67±6.377	2.933	0.291
Weight (kg)	76.40±10.370	74.27±8.738	2.133	0.547
BMI (kg/m^2)	25.43±3.659	25.50±2.746	−0.070	0.953
MUAC (cm)	30.07±2.789	29.27±2.251	0.800	0.395
ULL (cm)	74.60±5.166	72.73±4.543	1.867	0.302

Group 1: Euthyroid group, Group 2: Hypothyroid group, BMI: Body mass index, MUAC: Mid-upper arm circumference, ULL: Upper limb length

Table 2: Comparison of group mean visual and auditory reaction times. VRT and ART are expressed in ms

Reaction times	Group 1	Group 2	Difference of means	*P*
VRT	297.78±25.45	356.92±59.62	−59.14	0.001
ART	192.80±31.12	244.14±59.99	−51.34	0.006

Table 3: Comparison of group mean 2-back, 3-back, and 4-back task performance scores. Scores are expressed in percentage

n-back task	Group 1	Group 2	Difference of means	*P*
2-back	87.07±13.05	62.87±16.77	24.20	0.000
3-back	60.73±15.72	40.00±8.93	20.73	0.000
4-back	43.60±12.10	31.07±12.47	12.53	0.009

Table 4: Comparison of group mean serum T4, TSH, and testosterone levels. Serum titers of T4, TSH, and testosterone are expressed in nmol/L, μIU/ml, and ng/ml, respectively

Serum hormone assays	Group 1	Group 2	Difference of means	*P*
T4	99.91±13.52	73.22±31.43	26.69	0.005
TSH	2.93±0.86	34.14±37.58	−31.21	0.003
Testosterone	4.65±1.52	4.18±1.65	0.47	0.419

TSH: Serum thyroid hormones

n-back task scores, (v) serum T4 and visual-auditory reaction times, and (vi) serum T4 and n-back task scores.

DISCUSSION

In this study, sensory-motor coordination and working memory of a group of newly diagnosed hypothyroid males were assessed and their performance was compared to a group of age, education, and anthropometrically matched euthyroid, healthy males. Sensory-motor coordination was measured using simple reaction time and n-back task for working memory capacity. The diagnosis for hypothyroidism was based on the guidelines laid down by the American Association of Clinical Endocrinologists and American Thyroid Association.[12] The newly diagnosed hypothyroid group consisted of 4 overt hypothyroid cases (with serum TSH levels above 4.5 μIU/ml and low T4 levels), and 11 subclinical hypothyroid cases (with serum TSH levels between 4.5 and 10 μIU/ml and T4 levels within normal limits).[13] The serum testosterone levels of all 30 participants were within the normal range for the age group. A comparative analysis of both groups revealed that there was a statistically significant difference in the visual reaction time, auditory reaction time, and working memory scores, with the euthyroid group outperforming the hypothyroid group in all of these parameters. That is, the mean VRT and mean ART in the hypothyroid group were of a longer duration than the euthyroid group, and the percentage of correct responses on the 2-back, 3-back, and 4-back working memory tasks was higher in the euthyroid group than the hypothyroid group. Finally, the difference in the serum testosterone levels between both groups was not statistically significant. This result was expected since there exists no bi-way interaction in the pathways for the synthesis of the thyroid hormones and the androgen hormones.

Our results are consistent with the Shah and Nahar study[5] regarding reaction time and with the Zhu *et al.* study[8] regarding working memory. In the Shah and Nahar study, there was found to be a deficit in sensory-motor coordination as evidenced by the increased audiovisual reaction time using an indigenously designed Response Analyzer device. In the Zhu *et al*. study, functional magnetic resonance imaging (fMRI) was used to assess the working memory of euthyroid subjects, hyperthyroid patients using the digit n-back working memory task. Their results suggest that working memory at baseline is impaired in subclinical hypothyroidism and overt hypothyroid patients compared to the euthyroid subjects. However, after giving L-thyroxine-replacement therapy for 6 months to the hypothyroid group, both the memory performance and frontal executive functions improved. Smith *et al*. attributed to the efficacy of memory improvement with thyroid hormone replacement to the extensive inter-reliance between acetylcholine, nerve growth factor, and hippocampal function.[9] In a study by Muller, it was shown that low salivary testosterone levels are associated with increased mean reaction times in 64 young healthy males.[14] Cherrier *et al.* found that testosterone supplementation improved spatial and verbal memory in healthy older men between the ages 50 and 80 years.[15] Besides the executive (working memory) component of the brain, Gupta *et al.* have recently demonstrated the presence of abnormal wave latencies in their brainstem auditory evoked potential study of overt hypothyroidism, indicating that the metabolic derangement of the CNS caused by the lack of thyroid hormones extends to much deeper structures like the cochlea and auditory pathway

even in the absence of clinical evidence of hearing loss.[16] In our study, subjects belonging to the hypothyroid group with relatively higher levels of testosterone did not show better performance on the sensory-motor coordination and working memory tasks. Thus, our result shows that testosterone does not confer any specific neurocognitive protection against the effects of diminished levels of circulating thyroid hormones in male hypothyroidism.

However, the important results arrived at in this work must be viewed in the backdrop of certain study limitations. This was a study consisting of male subjects and it may or may not be correct to extrapolate our findings to females, owing to their distinctive thyroid and androgen hormone profile. The sample size of the hypothyroid group taken may not be of sufficient size to justifiably allow for generalization to a larger population of males. Physical activity is known to have a positive impact on attentional control, memory, and hormone profile. Hence, it is difficult to rule out the possibility of the concomitant influence of physical activity of the participants in affecting the results of our study. The number of subclinical hypothyroid subjects in our study exceeded the number of overt hypothyroid subjects. The thyroid hormones used for correlational analysis were serum total T4 and TSH levels only. Other thyroid hormones such as total T3, free T3, and free T4 were not included. However, each of these hormones have their own significant role to play in the maintenance of normal homeostasis in the body.

Future studies may be directed to toward studying attention and memory parameters in newly diagnosed overt hypothyroid subjects exclusively, with the help of modern neuroimaging techniques such as fMRI and electrophysiological attentional parameters like P300 wave characteristics of event-related potentials. This would in turn help strengthen the neuroanatomical and electrophysiological basis for diminished performance of hypothyroids compared to euthyroid on the reaction time and n-back tests. It would also help to confirm or rule out the supplementary role of testosterone in male hypothyroidism in the context of neurocognitive protection, and therefore, address the gender ratio disparity of the disease. However, any such proposed study must additionally include other thyroid hormones for correlational analysis such as serum total T3, free T3, and free T4, besides total T4 and TSH.

CONCLUSION

Our study demonstrates the lack of a specific neuroprotective role of testosterone against the effects of diminished levels of circulating thyroid hormones in male hypothyroidism.

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