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T_3 IS AS GOOD A POINTER OF CREATINE KINASE LEVELS IN EUTHYROIDS AS T_4 IS IN HYPOTHYROIDS

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ABSTRACT: Aim: Hypothyroidism is one of the commonest metabolic diseases which afflicts females more than males and is often associated with myopathy. Reports on relationship of muscle-markers with thyroid hormones in the (a) euthyroid population in general and (b) hypothyroid population in India are scarce. **Materials and Methods:** A randomized case-control study on the female population for which 60 hypothyroids and 30 euthyroid controls were selected. Total triiodothyronine (T_3), thyroxine (T_4), thyroid stimulating hormone (TSH) and two muscle markers - lactate dehydrogenase (LDH) and creatine kinase (CK) were measured from serum samples using automated analyzers. **Results:** CK was 71% higher and LDH 23.5% higher in hypothyroids than in euthyroid controls. CK correlated well with T_4 in hypothyroids (r= - 0.68, p<0.0001) and T_3 in euthyroids (r= 0.62, p= 0.003) but to a lesser extent with others viz. T_3 in hypothyroids (r= -0.46, p= 0.0002), T_4 in euthyroids (r= -0.49, p= 0.007) and TSH both in hypothyroids and euthyroids (r= 0.43, p= 0.0006; r= -0.40, p= 0.03 respectively). LDH correlated weakly with total T4 (p=0.28, r=0.03) in hypothyroids but showed no other statistically significant association.**Conclusions:** CK is satisfactorily indicated by total T_3 in euthyroid and T_4 in hypothyroid females. TSH is a weaker indicator.

INTRODUCTION: Hypothyroidism (HT) is one of the commonest metabolic disorders affecting 4 to 5% of the population in the developed world [1] and their confirmation with laboratory tests is generally required. Recent reports indicate that more than 10% of Indian adults are hypothyroids with prevalence being higher in females and older population [2] and the diametrically opposite disorder, hyperthyroidism, has a prevalence of just 1.8%. [3]

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Thus hypothyroids and euthyroids constitute most of the population. According to current guidelines of American Thyroid Association (ATA), the most "important and sensitive" laboratory test to identify primary HT is elevated levels of Thyroid stimulating hormone (TSH) in the blood. [4] Although TSH levels alone may not accurately represent the degree of HT, an elevated level is a very reliable criterion for diagnosis of primary hypothyroid state. [5]

In addition to a myriad of symptoms like weight gain, increased sensitivity to cold, fatigue, puffy face & hoarse voice, a large proportion of hypothyroid patients show neuromuscular symptoms and muscle weakness. The typical hypothyroid myopathy presents as mild weakness

of pelvic-shoulder girdle muscles. It can also manifest as polymyositis-like syndrome with proximal muscle weakness [6] and increased creatine kinase (CK) levels .[7]

Muscle damage is associated with the release of various "muscle markers" like CK and lactate dehydrogenase (LDH) .[8] CK shows heterogeneity across race and gender. [9] Reports on muscle markers in Indian hypothyroid population are not very well documented. This prompted us to study the association of CK and LDH with TSH, total T_3 and total T_4 in hypothyroids attending our hospital. We limited our study to females, the gender that is more likely to be afflicted by the disorder.

SUBJECTS AND METHODS:

This prospective study was conducted on OPD patients of a tertiary care hospital in Bangalore, Karnataka (Southern India) in the year 2014. The patient samples were randomly selected for the hypothyroid and euthyroid control group from those who had been advised estimation of T_3, T_4 and TSH. As further tests were performed on these pre-drawn samples, no consent was taken from patients. Although normal reference ranges of LDH levels in males and females are comparable (males: 135-225 U/L; females: 135-214 U/L), the same is not true for CK (males: 39-308 U/L; females: 26-192 U/L). HT being commoner in females, we selected only female subjects for the study. The normal reference levels (as per our hospital guidelines) of TSH, total T_3 and total T_4 are 0.34 and 5.6 µU/ ml, 1.3 to 2.87 nmol/ L and 77.9 to 156.5 nmol/ L respectively. 60 subjects who had a TSH level higher than the upper reference range were suspected to be hypothyroids and included in our study. 30 age matched euthyroids who had TSH levels within the normal range were included in the control group.

After overnight fasting, using standard aseptic precautions, 5ml of venous blood was collected in plain vacutainers and followed by chemical analysis which was done in fully automated analysers. Total T_3, total T_4 & TSH were analysed by the method of chemiluminisence assay in Beckman Coulter Access 2 (U.S.A.). Serum CK & LDH were analysed using 'International Federation of Clinical Chemistry and Laboratory Medicine' recommended methods in Cobas Integra 400 plus (Switzerland). The data collected was subjected to standard statistical analysis.

All groups passed normality (D'Agostino) test. Data was expressed as mean ± SD. Student's t-test was employed to compare parameters of controls with that of hypothyroids. Pearson's correlation was used to find relationships between parameters. A p value <0.05 was considered statistically significant. All statistical analysis were done using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

RESULTS:

60 hypothyroids and 30 euthyroids females were included in this study. Table 1 shows comparison of age, thyroid hormone and muscle marker levels between euthyroid controls and hypothyroids. Age was comparable between both the groups. Euthyroid controls had much lower levels of TSH in comparison to hypothyroids, whereas total T_3 and T_4 in hypothyroids were lower than that in controls. The abovementioned data is in accordance with the conventional knowledge of HT. CK in controls ranged from 41 to 150 IU/L (within normal range) & in hypothyroids from 22 to 388 IU/L (beyond normal range). Both in controls & hypothyroids, LDH crossed the upper limit of normal range: they ranged from 135 to 284 IU/L and 148 to 383 IU/L respectively. On an average CK was 71% higher and LDH 23.5% higher in hypothyroids than in euthyroid controls.

Correlation of thyroid hormones with CK in controls and hypothyroids was also analyzed as seen in Figure 1. Panels B, D and F display the results for euthyroid controls (n=30): T_3 shows a good positive, T_4 a moderate negative and TSH a moderate positive correlation with CK. Analogous results for Hypothyroids (n=60) are displayed in panels A, C and E: T_3 had a moderate negative, T_4 a good positive and TSH a moderate positive correlation with CK. The association with CK was strongest with total T_4 in the hypothyroid and total T_3 in the euthyroid group. LDH showed a statistically significant although weak association with total T_4 in the hypothyroid group ($r=0.28$, $p=0.03$). All other correlations of LDH with thyroid

hormones were statistically insignificant and are as follows: with T_3 in euthyroids (r= -0.2; p=0.2) and hypothyroids(r=0.2; p=0.1); with T_4 in euthyroids (r=0.1; p=0.4); with TSH in euthyroids (r=0.1; p=0.6) and hypothyroids (r= -0.09; p=0.5). The relationships between CK and LDH were also statistically insignificant both in the euthyroid (r= -0.1; p= 0.4) and hypothyroid group (r=0.1; p=0.5).

TABLE1: COMPARISON OF AGE, THYROID HORMONES AND MUSCLE MARKERS BETWEEN FEMALE HYPOTHYROIDS AND EUTHYROID CONTROLS.

Parameters	Euthyroids (n=30)	Hypothyroids (n=60)	*p* value
Age	35.2±6.8	38.5± 9.8	0.10
T_3 (nmol/ L)	1.74±0.24	1.37±0.49	0.0003
T_4 (nmol/ L)	122.4± 19.8	81.2± 43.4	< 0.0001
TSH (µU/ ml)	2.79±1.33	35.5± 23.2	< 0.0001
CK (U/ L)	102± 32	175± 79	< 0.0001
LDH (U/ L)	187± 38	231± 56	0.0002

Abbreviations- CK: Creatine Kinase; LDH: Lactate dehydrogenase;
TSH: Thyroid stimulating hormone; T_3: Triiodothyronine; T_4: Thyroxine.
All values are in Mean± SD

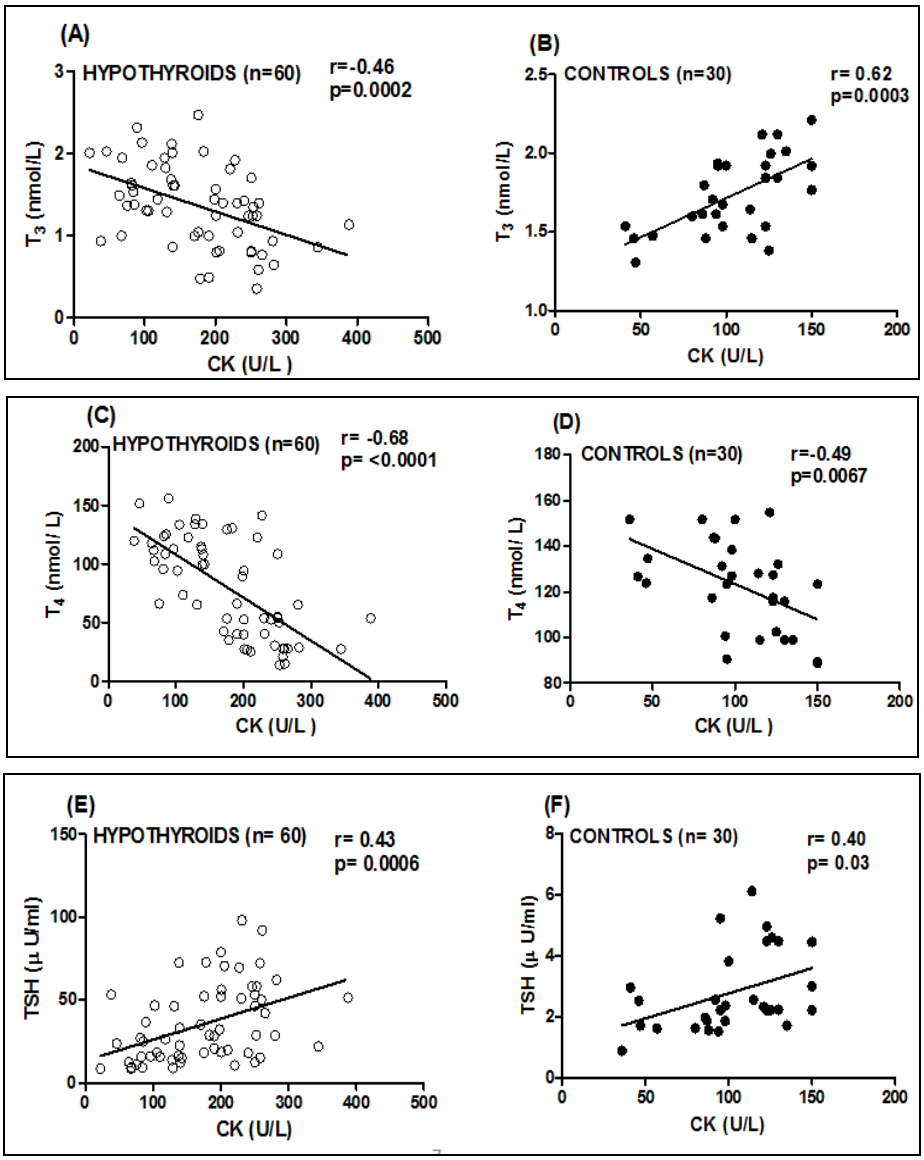

FIG.1: RELATIONSHIP OF CREATINE KINASE WITH (A) T_3 IN HYPOTHYROIDS, (B) T_3 IN EUTHYROID CONTROLS; (C) T_4 IN HYPOTHYROIDS, (D) T_4 IN EUTHYROID CONTROLS; (E) TSH IN HYPOTHYROIDS, (F) TSH IN EUTHYROID CONTROLS.

DISCUSSION: Associated myopathy is a common feature of most endocrine disorders, including HT, but is neglected as it is frequently not the presenting complaint. Also it is usually reversible with correction of hypothyroid state .[10]

It is well know that T_3 is biologically more active than T_4 but only a minor part of T_3 is produced directly by the thyroid gland. The major fraction is produced peripherally through deiodination of T_3, mainly by type 1 and 2 iodothyronine deiodinases (ID). The IDs are present in various tissues, but it has been shown that type 2 ID of skeletal muscles is the major converter of T_4 to T_3 both in euthyroid and hypothyroid state. [11]

Skeletal muscle itself is a target tissue for thyroid hormones action. [12] In hypothyroids, pain/cramps/stiffness of muscles are not uncommon and mild proximal muscle weakness (myopathy) occurs in more than a third of patients.[10] Biochemical abnormalities in hypothyroid muscle pivot around flawed energy production like faulty glycogen breakdown, defective enzymes and mitochondrial oxidative dysfunction Histochemical studies have shown atrophy and change in fast twitching type 2 muscle fibers to slow twitching type 1 muscle fibers in hypothyroids .[14] Damaged muscle fibers release "muscle markers" like CK and LDH into the blood stream and both have shown increased levels in hypothyroid myopathy. [15] It is also noteworthy that CK levels are higher in males and in individuals with greater muscle mass. [16]

Previous studies have shown that serum CK levels increase with increase in the degree of HT and that in hypothyroids CK shows a negative relationship with the levels of T_3 and T_4 .[7, 16] Our study which measures total T_3 and T_4 supports the same.

Another finding, which to the best of our knowledge has not been stressed upon previously, is that total T_3 levels show a good positive association whereas total T_4 shows moderate negative association with CK in euthyroids. The abovementioned relationship between CK and total T_3 is especially remarkable as a good statistically significant association was displayed in-spite of the smaller sample size of euthyroids. Thus our study indicates that (a) in hypothyroids, total T_4 is a satisfactory indicator of CK within or beyond its normal range and therefore a pointer of the degree of myopathy and (b) in euthyroids, total T_3 is an acceptable indicator of CK within the normal range. In South India, where the study was conducted, female hypothyroids have a prevalence of 11.5% and hyperthyroids of only 1.8%. [3] Thus we propose that once the thyroid status is known, thyroid hormones themselves have the potential of acting as an additional diagnostic tool for evaluation of CK levels in most of the female population. It might be noted that although recent ATA guidelines [4] recommend the measure of free thyroid hormones for diagnosis of thyroid conditions, the old practice of estimating total thyroid hormones is still followed in many laboratories due to logistic reasons.

The divergent directions of T_3 and T_4 in relation to CK in euthyroids point towards a relationship between the three. As a possible explanation, our preliminary suggestion is that in euthyroids, who have relatively undamaged muscles, elevated CK might be a partial reflection of increased muscle mass. We further make the assumption that larger mass of healthy muscle might result in a larger amount of type 2 ID and a consequential higher level of T_3. This appears physiologically reasonable because skeletal muscles themselves are a target tissue for thyroid hormone action. This assumption based explanation runs the danger of being inaccurate or an oversimplification. Larger and more elaborate studies to explore these findings are suggested.

This study also shows that both in euthyroids and hypothyroids, TSH shows only a moderate positive association with CK. This is in accordance with a previous report which indicates that although TSH has high accuracy for early diagnosis of HT, it is a poor measure for estimating the clinical and metabolic severity of primary HT. [5] Hypothyroids, in the study, did show an increased level of LDH (above 20%) when compared to euthyroids but the correlations of thyroid hormones with LDH were largely insignificant and much weaker than that of the same with CK. There are a number of limitations in this study. Free T_4 and other muscle markers like myoglobin were not measured. They

could have given the study higher precision and greater depth. Males and hyperthyroid females were not included, which if done, could have increased the reach of this study.

CONCLUSIONS: Total T_3 and total T_4 seem to be good indicators of CK levels in the majority of female population i.e. the euthyroid and hypothyroid women respectively. The third hormone of traditional thyroid profile, TSH, is a weaker indicator of CK.

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The authors have no conflicts of interest.

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