Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

Creatine kinase as a supportive test in thyroid disorders

Jincy W [1,2]*

1. Department of Biochemistry, ACS Medical College and Hospital, Maduravoyal, Chennai, India
2. Dr. MGR Education and Research Institute, Chennai, India
* Correspondence: Jincy W. Department of Biochemistry, ACS Medical College and Hospital, Maduravoyal, Chennai, India.
Tel: +918489471765, Email: jincynancy1994@gmail.com

Abstract

Background: Musculoskeletal disorders are common in patients with hypothyroidism, and are also observed in thyrotoxicosis. Creatine kinase (CK) is present in the muscles and is involved in energy metabolism. This study aimed to estimate the serum CK levels in patients with hypothyroidism, hyperthyroidism, and healthy individuals. Moreover, the correlation of CK levels with markers of thyroid function is assessed.

Methods: A total of 120 patients with hypothyroid and 120 with hyperthyroid were compared with 120 healthy individuals aged 20-60 years. The thyroid status was assessed by determining the serum thyroid-stimulating hormone (TSH) and free thyroxine (fT4) using chemiluminescent immunoassay. Serum CK was measured the by kinetic method. Statistical analysis was performed by analysis of variance and Pearson's correlation to investigate the correlations between CK and thyroid hormones.

Results: A significant increase (P<0.0001) and a significant decrease (P<0.0001) in serum CK were observed in hypothyroid patients (253.98±129.04 IU/L) and in hyperthyroid patients (34.68±13.15 IU/L), respectively, compared to the control group (72.9±29.01 IU/L). A negative correlation was found between fT4 and CK (r: -0.4253, P<0.0005).

Conclusion: It could be concluded that CK activity in serum may be a useful additional test in thyroid disorders.

Article History

Received: 6 March 2023
Received in revised form: 2 July 2023
Accepted: 6 April 2024
Published online: 28 April 2024
DOI: 10.29252/mlj.18.2.8

Keywords

Creatine kinase
Hypothyroidism
Hyperthyroidism

Article Type: Original Article

Introduction

Thyroid dysfunction is a common endocrine disorder affecting 5%-10% of individuals (1). Thyroid hormone plays a major physiological role in almost all the human body tissues. The energy metabolism of the cell is controlled by the thyroid hormone (2). Basal metabolic rate (BMR) increases by 60%-100% when thyroid hormone rises above normal. When no thyroid hormone is produced, the BMR may decrease to nearly half of the normal levels (3). It is also very necessary for growth and development, maintenance of normal cognition, cardiovascular functions, bone health, and tissue differentiation (3,4). The central nervous, cardiovascular, and skeletal systems are the major target tissues of thyroid hormones (5). The TRα1, TRβ1, and TRβ2 are the thyroid hormone receptors present in the body. In response to the release of T3, these receptors bind the ligand with a high affinity and regulate gene expression by acting as hormone-inducible transcription factors (6). Musculoskeletal disorders are often accompanied by thyroid dysfunction. In addition, they are also observed in thyrotoxicosis.

Creatine kinase (CK) levels are altered in both conditions (7). CK (EC 2.7.3.2; adenosine triphosphate: creatine N-phosphotransferase) is a dimeric enzyme (82 kDa) that catalyzes the reversible phosphorylation of creatine (Cr) by adenosine triphosphate (ATP). The active form of CK is a dimer composed of two subunits. Only three different pairs of subunits can exist as BB or CK-1, MB or CK-2, and MM or CK-3 (3,8-10). CK is considered to play an important role in the energetics of the cell. It is present near the motor proteins, ion pumps, and ATP-dependent processes. It acts as a fast ATP-regenerating enzyme (11). Serum CK has been used as a diagnostic tool in muscular dystrophy (12,13). Henceforth it was considered as an important clinical marker for muscle damage. The serum CK levels in healthy individuals depend on age, race, body mass, and physical activity (13).

In recent years, studies have evaluated the relationship of CK levels with thyroid diseases (1,7,13-19). Skeletal muscles are affected more profoundly in overt hypothyroidism than in subclinical hypothyroidism. The serum CK concentration declines in patients with hyperthyroidism and augments in patients with hypothyroidism. Therefore, the assay of serum CK activity may prove to be valuable in the screening of thyroid disorders. In the present study, we tried to evaluate the role of CK as an additional diagnostic tool in patients with thyroid disorders (1,7).

Methods

This study was conducted after obtaining ethical clearance from the Institutional Ethics Committee of Sri Ramachandra Medical college and Research Institute. The study consisted of 360 subjects who had requested thyroid profiles at Sri Ramachandra Hospital Laboratory Service, Sri Ramachandra University, Chennai. The study included the age group of 20-60 years. Subjects were categorized into three groups based on the serum levels of both thyroid-stimulating hormone (TSH) and free thyroxine (fT4). Serum TSH levels of 0.35-4 µIU/ml and fT4 of 0.8-1.8 ng/dl were regarded as control. TSH levels over 4 µIU/ml and under 0.35 µIU/ml were considered hypothyroidism and hyperthyroidism, respectively. Individuals with liver disease, muscle disease, cardiac issues, diabetes, renal dysfunction, pregnancy, thyroid medication usage, and drug abuse were excluded from the study. Healthy Individuals were considered as the control group and individuals with thyroid disorders but no other medical illness was regarded as cases.

The thyroid profile, namely serum TSH and fT4 of the study subjects were measured using kits from ADVIA Centuar chemiluminescent immunoassay system (20). The serum CK of the participants was assayed using kits and a semi-automated analyzer based on the kinetic method (21). A volume of 3 ml of venous blood was obtained for investigations taking all aseptic precautions. The serum was separated and investigated either immediately or it was preserved at 2°C-8°C for up to 7 days for CK measurement. The results were expressed as mean ± SD. Statistical analysis was completed by analysis of variance (ANOVA) followed by Tukey HSD multiple range test. The correlation coefficient (r value) was calculated between thyroid function tests and CK for all groups by Pearson's correlation.

Results

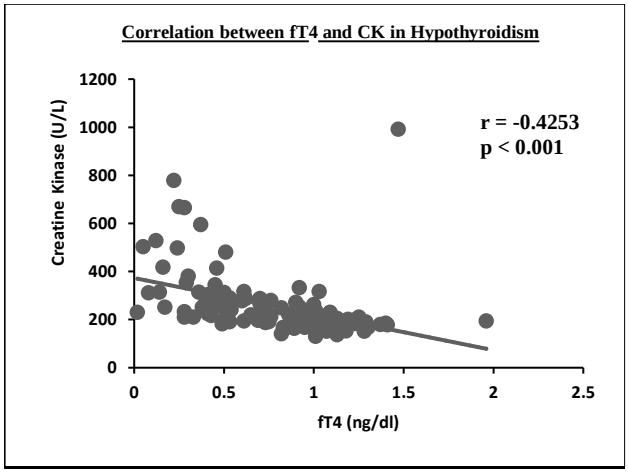
A significant increase (P<0.0001) and decrease (P<0.0001) in serum CK was observed in patients with hypothyroidism (253.98±129.04 IU/L) and hyperthyroidism (34.68±13.15 IU/L), respectively, when compared to the control group (72.9±26.10 IU/L) as shown in Table 1. A negative correlation was found between fT4 and CK (r: -0.4253, P<0.0005). Values were expressed as mean ± SD (n=120 per group). Statistical analysis was performed by ANOVA followed by Tukey HSD multiple range test (P<0.0001).

Table 1. Comparison of levels of serum TSH, FT_4 and CK in control, hypothyroidism and hyperthyroidism

GROUP	AGE (Years) (n=120)	TSH (µIU/ml) (n=120)	fT4 (ng/dl) (n=120)	CK (U/L) (n=120)
Control	37.08±12.01	1.93±0.91	1.17±0.15	72.9±26.10
Hypothyroidism	37.46±11.25	51.38±49.76*	0.79±0.36*	253.98±129.04*
Hyperthyroidism	36.94±11.02	0.08±0.08*	1.70±0.80*	34.63±13.15*

* P<0.0001

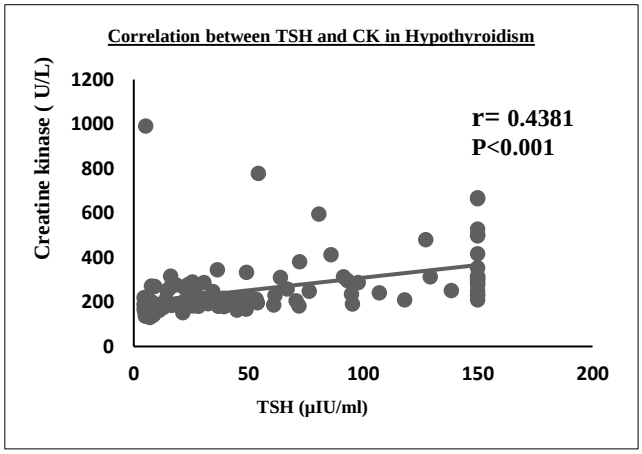
In correlation between Serum fT4 and CK in Hypothyroidism a significant negative correlation was shown between serum fT4 and serum CK (r: - 0.4253, P<0.001) in hypothyroidism (Figure 1).



P = < 0.001 (Highly significant)

Figure 1. Correlation between serum fT4 and serum creatine kinase in hypothyroidism

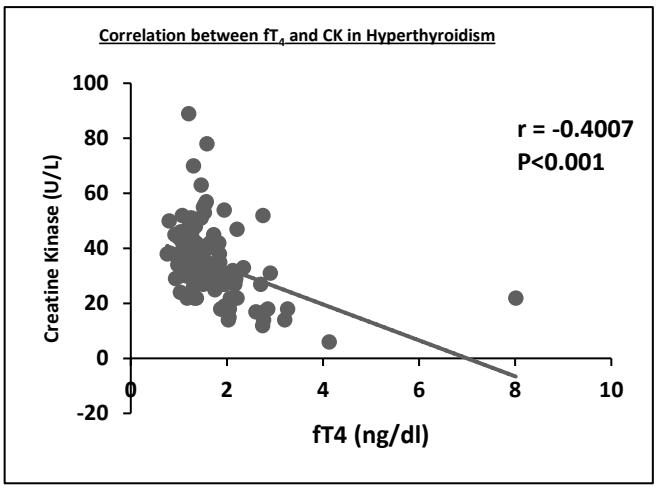
In correlation between Serum TSH and CK in Hypothyroidism a positive correlation was obtained between serum TSH and CK (r: 0.4381, P<0.001) in hypothyroidism (Figure 2).



P = < 0.001 (Highly significant)

Figure 2. Correlation between serum TSH and serum CK in hypothyroidism

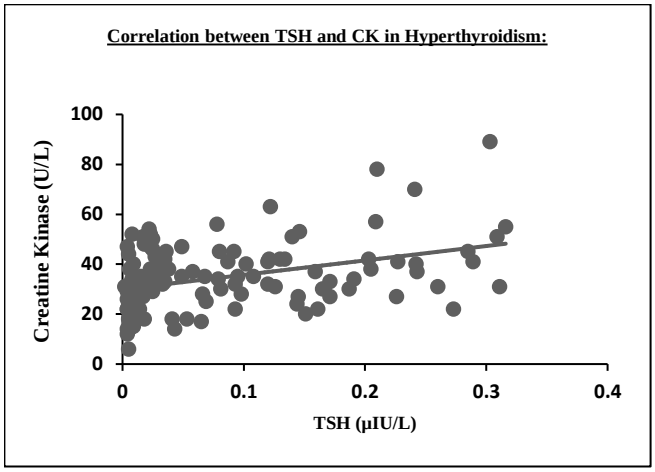
In correlation between Serum fT4 and CK in Hyperthyroidism a significant negative correlation was obtained between serum fT4 and CK (r: -0.4007, P<0.001) in hyperthyroidism (Figure 3).



P<0.001 (highly significant)

Figure 3. Correlation between serum fT4 and CK in hyperthyroidism

In correlation between serum TSH and CK in Hyperthyroidism a positive correlation was observed between serum TSH and serum CK (r: 0.3863, P<0.001) in hyperthyroidism (Figure 4).



P<0.001 (Highly significant)

Figure 4. Correlation between serum TSH and CK in hyperthyroidism

Discussion

The present study evaluated the role of CK as an additional parameter for hypothyroidism and hyperthyroidism. In the study, the serum CK activity was markedly increased in patients with hypothyroidism when compared to normal individuals. This shows the involvement of CK in thyroid disorders (1,7,14). A positive correlation was obtained between TSH and serum CK activity. Similar results were reported in several studies showing a positive correlation between TSH and CK activity (14,15). There was a negative correlation between fT4 concentration and serum CK activity in this study. Hekimsoy et al. (2005) found that hypothyroidism had effects on the skeletal muscle. He compared overt hypothyroidism and subclinical hypothyroidism and proved that skeletal muscle was affected more in overt hypothyroidism (17). DA McGrowder et al. (2011) showed that the increased activity of CK-MM was seen in patients with hypothyroidism which was also confirmed with other previous studies (14).

Very high levels of CK and symptoms of myositis were resolved after treatment for hypothyroidism. Patients undergoing total thyroidectomy for Grave's disease developed myalgia with a high level of CK. The clinical features and CK levels were normalized after treatment and reappeared after the cessation of treatment. Therefore, it can be concluded that muscles are involved in thyroid disorders (7). The marked myopathy along with associated histological changes of muscle cells was seen in patients with primary hypothyroidism (19). Docherty et al. (1984) demonstrated that serum myoglobin and CK were sensitive early detectors of muscle disorder in hypothyroid myopathy (19).

In hypothyroidism, CK leaks from cells as a result of increased cell permeability, which is due to an alteration in the sarcolemmal membrane (1,13,21). Hypothyroidism being a hypo-metabolic state is significantly associated with decreased ATP production due to a reduction in glycolysis and oxidative phosphorylation (1,14), leading to subnormal body temperature which causes enzyme leakage from the muscle cells (14,22). Non-specific muscle stiffness related to myalgia may be associated with elevated serum muscle enzyme. In addition, reduced turnover in serum can also lead to augmented CK activity in hypothyroidism (14).

Hyperthyroidism can cause increased stimulation of glycolysis and oxidative phosphorylation which produce high amounts of ATP, resulting in the increased utilization of CK from the muscle cells (1,14). Furthermore, studies have shown that in hyperthyroidism the CK efflux will not be seen due to the lower permeability of the muscle cells. Increased turnover of CK in a hyper-metabolic state may also contribute to low CK activity (1,7,14). The results are as expected because both CK and fT4 are involved in maintaining energy metabolism. The alteration in serum CK levels observed in thyroid disorder indicates that serum CK can be used additionally along with the thyroid parameters to evaluate muscle involvement.

Conclusion

Significant increases and decreases were observed in the serum CK in hypothyroid and hyperthyroid patients, respectively, compared to the control group. A study on the assay of CK activity in serum may be a useful additional test for thyroid disorders. An inverse correlation between fT4 and CK supports the evidence that both fT4 and CK were involved in energy metabolism.

Acknowledgement

The authors would like to thank Dr. Nalini Ganesan (Former Professor of Biochemistry, SRMC&RI), Dr. Archana. A. (Professor and HOD, Department of Biochemistry, ACSMCH), Dr. Sathiya Priya. V. (Associate Professor, Department of Biochemistry, ACSMCH).

Funding sources

The authors of this article did not receive any financial support for the research.

Ethical statement

I got ethical clearance from SRMC & RI. Attach the ethical clearance and consent form. REF: CSP/15/SEP/43/50.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

All authors have contributed equally.

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How to Cite:

Jincy W. Creatine kinase as a supportive test in thyroid disorders. *Med Lab J.* 2024;18(2):8-10.