National Journal of Basic Medical Sciences ORIGINAL ARTICLE Volume - III, Issue-2

AN APPROACH TO EARLY DETECTION OF THYROID DYSFUNCTION ASSOCIATED WITH MYOPATHIES

G.Rupa[1], G.Assalatha[2], N.Geetha[3]

ABSTRACT

Background: The altered serum levels of triiodothyronine (T3) and thyroxine(T4) in thyroid disorders is well established but the correlation of CPK (Creatine Phospho Kinase) with thyroid dysfunction is not.

Aims and objectives: To confirm definite changes in CPK levels alter functions of thyroid gland and establish serum CPK level estimation as a valid indicator of thyroid dysfunction; and suggest it as a screening test to differentiate hyper/hypothyroid myopathies.

Materials and methods: Fifty hyper/ hypothroid female patients (from reproductive age group) in a Thyroid Clinic (July-December, 2005) were selected. Fifty controls matching in age/sex were also included. Parameters studied include BMI, serum CPK (Autozyme UV kinetic method), serum T3, T4, TSH (RIA), serum cholesterol, FBS and PPBS.

Results and analysis: Statistical analysis was done using SPSS Windows version 10 and association among the variables were assessed using Pearson Chisquare test. In hypothyroid patients, T3/T4 serum levels were found lowered with increased TSH levels(100%) along with marked rise in CPK levels(84%) whereas hyperthyroid cases showed an increase(T3/T4 serum levels) with decrease in TSH(96%) and CPK levels; and thus confirming, an inverse relation between Serum CPK levels and T3/T4 levels.

Conclusion: Hypothyroidism reduces ability of muscles to maintain its energetic economy leading to myopathy causing elevation of CPK levels while a decrease in the generation of enzyme is the cause in hyperthyroidism. Thus myopathy may be the sole clinical manifestation in altered thyroid states suggesting that all patients with unexplained muscular symptoms should be screened for thyroid dysfunction with serum CPK.

Keywords: Creatine Phospho Kinase,Thyroid dsfunction,Myopathies.

INTRODUCTION

In recent years studies have been conducted to establish a relationship of CPK levels in thyroid disease.A majority of patients with hypothyroidism have been shown to have an increased serum CPK.The exact etiology is not known.Thus the assay of CPK activity in serum is extremely valuable in screening thyroid dysfunction and in present study an attempt has been made to correlate CPK levels with T3,T4 and TSH in hypo and hyperthroidism.[1]

Occult thyroid dysfunction prevails in a major population and that myopathy is a common associate of hypo/hyper functioning of the gland.Much research has been done to elucidate how thyroxine affects muscle function.Thyroid dysfunction causes a constellation of changes in the body which resuls in altered metabolic functions that occurs in many organ systems including muscle.[2]The duration and degree of thyroid dysfunction definitely determines the severity of myopathy[3].Although diagnosis can be tricky this disorder is reversible with appropriate treatment.Therefore the key to ealy diagnosis is to maintain a high index of suspicition and to readily screen for the presence of abnormal thyroid function.

From this work has developed a greater understanding of the rationale for the choice of enzyme markers to be used in diagnostic tests. Among the various enzyme markers CPK shows the highest activity in skeletal muscles.Apart from being the best biochemical marker of myopathies;it has also other advantages.Being a very sensitive low cost method,which is unaffected by hemolysis,this test is very easy to perform[4].The aim of the study is to confirm the definite changes in CPK levels with altered functions of thyroid gland and hence this enzyme marker can be introduced as a screening test to differentiate

[1]Assistant Professor, Department of Physiology, [2]Joint Director, Department of Medical Education
[3]Additional Professor, Department of Physiology, Govt. Medical College, Thiruvananthapuram, Kerala-695011

myopathies .Hence this study is undertaken with the hope that this can provide us with hidden clues which may be revealed only very late otherwise.

MATERIALS AND METHODS

A minimum of fifty hyper/ hypothroid female patients in the reproductive age group attending the thyroid clinic which was diagnosed by the endocrinologists from july 2005 to december 2005 were selected for the study. Age and sex matched fifty controls were also included in the study.The study protocol was approved by the Ethical Committee of the institution.The parameters studied include body mass index,serum CPK (Autozyme UV kinetic method),serum T3, T4,TSH(RIA),serum cholesterol,FBS,PPBS.

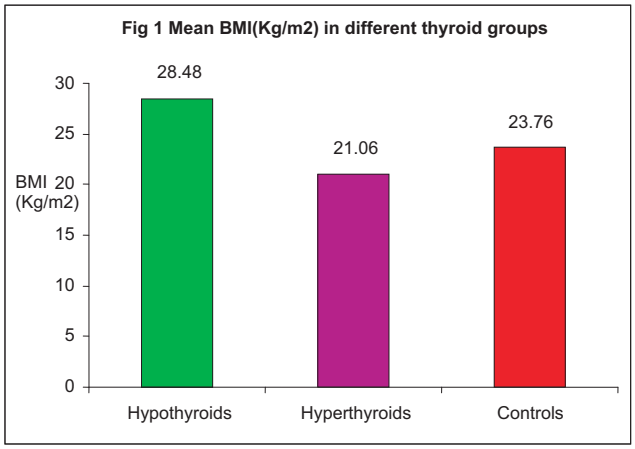
Screening was done based on a proforma. Detailed history was noted in proforma. Blood pressure was recorded. Patients were adviced to come fasting overnight and precautions, 8ml blood was withdrawn from each patient. 3 ml blood was taken in a clean plain glass bottle for the estimation of serum CPK and serum total cholesterol. Blood was allowed to clot and serum was separated by centrifugation.Another 3ml was taken in a plain glass bottle for the estimation of T3, T4 and TSH. Blood was allowed to clot and serum was separated by centrifugation and stored at 20oc to be assayed at a later state.

Principles of CPK estimation is based on the fact that Creatine kinase catalyzes the conversion of creatine phosphate and ADP to creatine and ATP. ATP phosphorylates glucose to Glucose 6 PO4 in the presence of the enzyme Hexokinase. Glucose 6 PO4 is oxidized to 6 phosphogluconate reducing NADP to NADPH in the presence of G-6-P DH (Glucose 6PO4 dehydrogenase). The rate of increase in NAPH absorbance at 340 nm was directly proportional to the activity of creatine phosphokinase in serum/plasma.Blood should be collected in a clean dry container. The samples should be brought to room temperature prior to use. Prewarmed at 37°C the required amount of working solution before use .Mixed thoroughly and transferred the assay mixture immediately to the thermostated Cuvette and started the stop watch simultaneously. Recorded the first reading at 180th second. Subsequently four readings with 30 second interval at 340 nm.

RESULTS AND ANALYSIS

Statistical Analysis

For analysis, SPSS 10.0 Version was used. Association among variables were assessed using Pearson Chi-Square test.

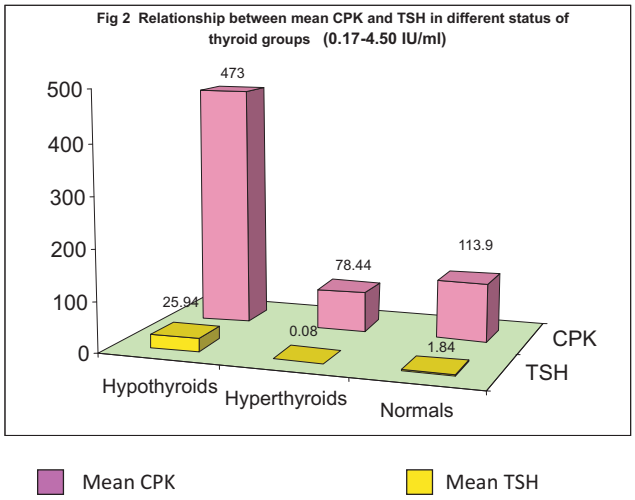


Hypothyroids had BMI much higher than normals while in hyperthyroid patients, it was slightly lower than in normals.

Table 1 Distribution of cases and Controls as per Serum CPK levels

CPK	Hypothyroids	Hyperthyroids	Controls	Total
Normal	4 (16.00%)	24 (96.00%)	49 (98.00%)	77 (77.00%)
High	21 (84.00%)	1 (4.00%)	1 (2.00%)	23 (23.00%)

Chi square = 70.037, p = 0.000 Very highly significant



Direct correlation was noticed in case of hypothyroidism in the levels of TSH and CPK. CPK levels were below normal in hyperthyroidism with a concommitant decrease in TSH.

Table 2 T test comparing hypothyroids and hyperthyroid of different parameters

		Mean	SD	*t value*	*p value*
Age	Hypothyroids Hyperthyroids	31.76 31.64	8.32 9.04	0.049	> 0.05
Height (cm)	Hypothyroids Hyperthyroids	156.04 157.52	4.82 4.05	-1.175	> 0.05
BMI (Kg/m2)	Hypothyroids Hyperthyroids	28.48 21.06	3.61 1.68	9.306	< 0.001
Weight (Kg)	Hypothyroids Hyperthyroids	69.24 52.12	8.22 4.55	9.114	< 0.001
T3	Hypothyroids Hyperthyroids	0.31 4.31	0.21 2.89	-6.907	< 0.001
T4	Hypothyroids Hyperthyroids	34.28 168.80	8.91 24.65	- 25.657	< 0.001
TSH	Hypothyroids Hyperthyroids	25.94 0.08	26.49 0.10	4.881	< 0.001
CPK	Hypothyroids Hyperthyroids	473.00 78.44	262.95 43.09	7.404	< 0.001

Table 3 Present History – Myopathy : Muscle Pain

	Hypothyroids	Hyperthyroids	Normals	Total
Nil	3 (12.00%)	6(24.00%)	50 (100.00%)	59(59.00%)
Mild	12 (48.00%)	19(76.00%)	-	31(31.00%)
Moderate	8 (32.00%)	-	-	8 (8.00%)
Severe	2 (8.00%)	-	-	2 (2.00%)

Chi square = 92.958, p = 0.000 Very highly significant

Table 4 Present History – Myopathy : Fatigue

	Hypothyroids	Hyperthyroids	Normals	Total
Nil	7 (28.00%)	17 (68.00%)	50 (100.00%)	74 (74.00%)
Mild	9 (36.00%)	8 (32.00%)	-	17 (17.00%)
Moderate	7 (28.00%)	-	-	7 (7.00%)
Severe	2 (8.00%)	-	-	2 (2.00%)

Chi square = 55. 955, p = 0.000, Very highly significant

Table 5 Present history – Myopathy : Exercise Intolerance

	Hypothyroids	Hyperthyroids	Normals	Total
Nil	13 (52.00%)	24(96.00%)	50 (100.00%)	87(87.00%)
Mild	9 (36.00%)	1(4.00%)	-	10(10.00%)
Moderate	2 (8.00%)	-	-	2 (2.00%)
Severe	1 (4.00%)	-	-	1 (1.00%)

Chi square = 36. 524, p = 0.000 Very highly significant

Table 6 Present History – Myopathy : Gradual onset

	Hypothyroids	Hyperthyroids	Normals	Total
Nil	16 (64.00%)	20(80.00%)	50 (100.00%)	86(86.00%)
Mild	6 (24.00%)	5(20.00%)	-	11(11.00%)
Moderate	3(12.00%)	-	-	3(3.00%)

Chi square = 22. 833, p = 0.000 Very highly significant

DISCUSSION

Hyper and hypothyroidism together account for considerable morbidity. The total prevalence of these two disorders in adults is estimated to be 1-4% and the prevalence being higher in women and increases with increasing age (Dos Remedios, Weber)[5].

Pathophysiology of Hypothyroid Myopathy : Myopathy may be the sole clinical manifestation of hypothyroidism; suggesting that all patients with unexplained muscular symptoms should be screened for thyroid dysfunction. Muscle symptoms are very prevalent and include myalgia, weakness, mainly symmetrical and proximal, stiffness, cramps and easy fatigability (Degroot)[6].

Hypothyroidism can induce a metabolic myopathy especially of the mitochondrial metabolism. The metabolic myopathies result in a fall in muscle energy production (Diana)[7]. Thyroid hormone affect the expression of MHC (Myosin heavychain) genes in the skeletal muscle as well as cardiac muscle. Conversely the expression of alpha MHC is depressed and that of beta MHC is enhanced in hypothyroidism leading to reduction in the speed of contraction. So a shift of alpha MHC to increased beta MHC therefore brings about decrease in energy consumption, which ultimately causes a shift of muscle fibre type from fast to slow twitch (Ganong)[8].There is global inhibition of main oxidative pathways within the cells. Trans sarcolemnic transport is impaired and there is reduction in muscle mitochondrial oxidative capacity. Biochemical substrate of these

complaints is partly provided by a rise in the inorganic PO_4/ ATP ratio in the resting muscle with a greater fall in intracellular pH.

All these factors contribute to muscle weakness, fatigue and excertional pain. Exercise intolerance could be due to an abnormal recruitment of several metabolic pathways such as glycolysis related to the mitochondrial metabolism impairment. Abnormal accumulation of protons and monovalent phosphate ions which are involved in the actin – myosin interaction as well as abnormal Calcium metabolism can also be the causes of exercise intolerance (Diana)[7].The most common laboratory abnormality indicative of patients with hypothyroidism is a high serum creatine phosphokinase concentration (Sterling)[9]. The source of the enzyme appeared to be skeletal muscle which is consistent with myopathy seen in hypothyroidism (Joet Goldman et al 1977)[10].The metabolism was decreased (leading to elevation of creatine phosphokinase) in hypothyroidism and increased (leading to reduction of creatine phosphokinase) in hyperthyroidism (Stephen)[11] These enzymatic levels should be documented in patients with severe hypothyroidism; requiring treatment with thyroxine (Orlo)[12].

The slow time course increase in CPK appears to be a true reflection of efflux from the muscle rather than a slow clearance from either the muscle itself or the circulation. The magnitude of efflux depends upon the mechanical damage to the cell membrane. This may also be exacerbated by metabolic disturbances such as calcium leakage from the damaged sarcoplasmic reticulum (Karin Harms)[13].However the normal function of CPK is not evident in normal situation and it becomes relevant only when damage occurs to the muscle. During the process of muscle damage; the muscle cells break open and their contents find their way into the blood stream. Since most of the CPK in the body normally exist in the muscle; a rise in the amount of CPK in the blood indicates that muscle damage has occurred (Seigel)[14]. Here it should be emphasized that elevation of creatine kinase seldom occurs in other myopathies. Probably membrane integrity is lost only in hypothyroid myopathy.

Therefore the mechanism underlying elevation of CPK includes muscle fiber degeneration,altered muscle energy metabolism,decreased clearance of CPK from circulation, decreased metabolism of creatine kinase(Werner)[15]. So to conclude in hypothyroid patients T3,T4 levels in serum were found to be lowered with an increase level of TSH associated with marked rise in serum CPK level. Thus the serum CPK show an inverse relation with serum T3, T4 levels (Rati Mathur 2003)[1]

Pathophysiology of Hyperthyroid Myopathy: Muscle weakness tend to vary from patient to patient and is roughly proportional to the severity and duration of the disease than its biochemical severity (Williams)[16].Generally associated with easy fatiguability and varying degrees of muscular atrophy.In certain hyperthyroid cases involvement of muscles is associated with wasting that again tends to be proximal and is out of proportion to the overall weight loss. (Thyrotoxic myopathy).

Excess thyroid hormone has catabolic effects on muscle with negative nitrogen balance being a consistent finding in virtually all studies. This loss of muscle mass provides a ready explanation for both the subjective and objective muscle weakness that is so common in patients with thyrotoxicosis. Additional adverse effect of excess thyroid hormone may be related to hormone's effects on the transcription of genes controlling calcium regulatory proteins and myosin heavy chain synthesis in the muscle. Sensitivity of tissue to catecholeamines is increased. The muscle activity shows altered electrical response and increased metabolism (Ganong)[8]. In muscles substrate uptake and utilization are increased, but the latter is less efficient than normal. Therefore ATP generation and muscle contractility are decreased (Werner)[15].

Chemical analysis of creatine and phosphorcreatine in muscles of hyperthyroid patients reveal a decrease in both substance (Wang)[17]. Spontaneous creatinuria occurs in most patients with hyperthyroidism and tolerance to the ingested creatine is decreased in all of the untreated cases(Thorn)[18]. Thyroxine inhibits the phosphorylation of creatine invitro. This might explain the creatinuria of the thyrotoxic patient (Leslie De Groot).[6] Mitochondria are the power stations and swelling induced by the excess hormone ultimately paralayses the oxidative phosphorylation systems due to reduced availability of ATP and creatine phosphate.

- Among the muscle mass, thyrotoxic myopathy has a special preference for extensor group, which contain a large proportion of red muscle fibres.

- Red muscle have increased number of mitochondria.
- Coupling (biological oxidation + oxidative phosphorylation) is necessary for the release of energy during muscle contraction.
- Excess T4 produces uncoupling of oxidative phosphorylation and hence simultaneous ATP production fails to occur.
- Contraction of muscle fibres, the result of interaction of actin, myosin and ATP progressively fails due to depletion of amount of available ATP.

The net effect is muscles show contraction weakness and lack of normal contraction potentiation (Gabriel)[19].So in hyperthyroid patients serum levels of T3, T4 were found to be increased with decrease in TSH with normal or sometimes reduced CPK. The myopathy associated with hyperthyroidism showed proximal weakness (80%) distal weakness 20%, occasional myalgias associated with brisk reflexes and normal or reduced CPK (Steven)[20].

SUMMARY AND CONCLUSION

Thyroid dysfunction has a definite role in myopathy. Both hyperthyroidism and hypothyroidism can present with myopathy. Thyroid plays a definite role in the metabolism of creatine. Any threat to the integrity of sarcolemma will cause an elevated serum CPK levels due to its leakage to the outside. Hence the enzyme levels is definitely increased in myopathies. Patients with hypothyroidism show an elevated level of the enzyme, while in those with hyper functioning, the levels of CPK was normal or decreased. The decreased values were associated with severe degrees of hyper thyroidism. Accumulation of serum CPK in the muscle sarcoplasm, in excess than normal along with membrane damage explains elevated levels of enzyme in hypothyroidism, while a decrease in the generation of the enzyme is the cause in hyperthyroidism. Hence from the results of the present study, it can be recommended that all patients with myopathies should be routinely screened for thyroid dysfunction.

In this context, estimation of serum CPK levels gains attention by the fact that, it can distinguish between the two altered states of thyroid gland both of which upon treatment will revert the patient back to normalcy. Hence this enzyme marker is very valuable to the physician, as it throws light on the definite pathway he has to follow for a correct treatment. Though sophisticated this marker is within the reach of common man also; hence it is of utmost importance to man kind.

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