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Original Research Article

Prevalence of Clinically and Biochemically Diagnosed Myopathy in Hypothyroid Patients

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Abstract

Background: In this study, we wanted to estimate the proportion of myopathy among hypothyroid patients, assess the correlation of hypothyroid myopathy with Serum TSH levels, and study the association of anti-TPO antibody with hypothyroid myopathy.

Methods: This was a hospital-based cross-sectional study conducted among 100 patients who presented with hypothyroidism to the Thyroid Clinic, Department of Internal Medicine, Government Medical College, Thiruvananthapuram, for one year, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results: Hypertension has got a statistically significant relation with hypothyroid myopathy ($p=0.013$). Increased sensitivity to cold ($p<0.001$) and depression ($p=0.004$) when compared to other symptoms of hypothyroidism has got significance in hypothyroid myopathy. Proximal "Limb-Girdle" weakness of upper limbs is much more common in hypothyroid myopathy as per the study ($p<0.001$). Among the serum muscle enzymes studied, there exists a statistically significant relation between S. CPK ($p<0.001$) and S. LDH ($p=0.029$) with hypothyroid myopathy. Urine myoglobin has a statistically significant relation with hypothyroid myopathy ($p<0.001$). There is a statistically significant relation between anti-TPO and hypothyroid myopathy in the study ($p<0.001$). Anti-TPO and S. CPK have a statistically significant linear relationship ($r=0.812$, $p<0.001$) in the study.

Conclusion: The prevalence of myopathy in overt hypothyroidism is 69% in the study. Serum TSH levels and serum muscle enzymes CPK, LDH, and urine myoglobin have a significant correlation with hypothyroid myopathy. Anti-TPO has a significant relation with hypothyroid myopathy, and it has a significant positive linear relationship with CPK values.

Keywords: Hypothyroid Myopathy, S.TSH, S. CPK, S. LDH, Urine Myoglobin, Anti-TPO.

Introduction

Hypothyroidism is an endocrine disorder which affects up to 5% of the general population. Primary hypothyroidism constitutes over 99% of affected individuals. The most common cause of all thyroid disorders worldwide, including hypothyroidism is environmental iodine deficiency. Hashimoto's disease (chronic

autoimmune thyroiditis) is the most common cause of thyroid failure in areas of sufficiency. The diagnosis of hypothyroidism as overt primary hypothyroidism is by a serum thyroid-stimulating hormone (TSH) concentration above and thyroxine concentration below the normal reference range. Symptoms of hypothyroidism are non-specific. It includes mild to moderate weight gain, fatigue, poor concentration, depression, and menstrual irregularities. The consequences of untreated or under-treated hypothyroidism include cardiovascular disease and increased mortality. [1] Myopathies are disorders affecting the channel, structure or metabolism of skeletal muscle. [2] Muscle weakness, aches and cramps, stiffness and delayed tendon jerk relaxation are the usual features of hypothyroid-associated myopathy. [3] Possible mechanisms for myopathy seen in hypothyroidism include an autoimmune reaction affecting the muscle, infiltration by "myxedema", or a disorder of the muscle membrane. Thyroid deficiency likely affects muscle cells directly. Muscular hypertrophy with muscle stiffness in hypothyroidism is seen in less than 10% of cases. [4] Serum CPK activity is frequently elevated in patients with hypothyroidism. In most cases, the associated muscle disease is mild. Rarely, hypothyroidism is associated with severe skeletal muscle affection and rhabdomyolysis. [5,6] CPK elevation may be due to direct cell damage, down regulation of the cellular metabolism or due to a reversible defect in glycogenolysis. [7–9] There are indications that the severity of hypothyroidism is correlated with the degree of CPK elevation, [9] but it is not known if the severity of the symptoms correlates with the degree of CPK elevation. Hashimoto's thyroiditis is an autoimmune disease characterized by the destruction of thyroid cells by cell and antibody-mediated immune processes. It contributes to the most common cause of hypothyroidism in developed countries. Raised thyroid-stimulating hormone (TSH) and low free thyroxine (FT4) levels, along with increased antithyroid peroxidase (TPO) antibodies are the common lab findings. Fatigue, exertional dyspnoea, and exercise intolerance are mostly associated with a combination of limited pulmonary and cardiac reserve. In addition to that decreased muscle strength or increased muscle fatigue will be present. Biochemical changes in this group are as follows: Diminished fatty acid mobilization, increased utilization of glycogen stores, and decreased muscle oxidation of pyruvate and palmitate. Muscle weakness and myopathy are important features. [10]

Aims and Objectives

- To estimate the prevalence of clinically and biochemically diagnosed myopathy among hypothyroid patients attending the Thyroid Clinic of Govt. Medical College, Thiruvananthapuram.
- To compare the clinical and biochemical parameters (TSH, FT4, CPK, LDH, SGOT, urine myoglobin and anti-TPO) among hypothyroid patients with and without myopathy.
- To study the relation of anti-TPO antibody with hypothyroid myopathy.

Methods

This was a hospital-based cross-sectional study conducted among 100 patients who presented with hypothyroidism to the Thyroid Clinic, Department of Internal Medicine, Government Medical College, Thiruvananthapuram, for one year, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

All patients with hypothyroidism - S. TSH > 10 mIU/L; not on treatment.

Exclusion Criteria

- Patients who were not consenting to the study.

- Patients without hypothyroidism.
- Subclinical hypothyroidism, Drug-induced or Secondary Hypothyroidism.
- Those taking Statins, Alcohol, Corticosteroids, Local injections of narcotics, Colchicine, and Chloroquine.
- Any endocrine disorder other than hypothyroidism.
- Recent tropical fever or electrolyte imbalance.

Sample Size

Calculated using the formula.

$N = [(Z_{1-\alpha/2})^2 x\ P\ x\ Q] / d^2$

Where,

$Z_{1-\alpha/2} = 1.96$ at a 5 % level of significance

P = Proportion of clinically diagnosed myopathy = 60%

Q = 100 – P = 40%

d = 20% of P

So, $N = (1.96)^2 x\ 60\ x\ 40 / (20\%\ of\ 60)^2$

Study Procedure

After obtaining clearance from the institutional ethics committee, all consecutive cases that satisfied the inclusion criteria and consent to take part in the study were recruited.

A structured Proforma was used to collect relevant history, and physical examination and 5ml of the plain blood sample was collected for the investigations: S.CPK, S.LDH, SGOT, ANTI-TPO and 5ml of a urine sample for urine myoglobin levels and sent to biochemistry lab for estimation as follows:

Analyte	Sample	Method	Instrument
TSH	Serum	Access Hypersensitive hTSH Assay	Beckman Access 2 Immunoassay Analyzer
FT4	Serum	Access Free T4 assay	
Anti-TPO	Serum	Access TPO antibody assay	
CPK	Serum	Enzymatic Colorimetry	Beckman Coulter AU 680
LDH	Serum	Enzymatic Colorimetry	
SGOT	Serum	Enzymatic Colorimetry	
Myoglobin	Urine	Chemiluminescent Microparticle Immunoassay	Architect stat

In this study, all patients recruited were having Overt Hypothyroidism with S. TSH levels > 10mIU/L with a subnormal FT4 according to ATA/AACE Guidelines for Hypothyroidism. [11] The clinical and biochemical diagnosis of myopathy was then established in hypothyroid subjects using the criteria mentioned in the Muscle diseases chapter of Continuum, American Academy of Neurology. [12]

The proportion of myopathy in hypothyroidism was then assessed and the lab parameters were compared in those with and without myopathy.

Statistical Methods

Data were entered into an excel sheet. Data analysis was done using IBM SPSS software version 26. Categorical variables were expressed as proportions and quantitative variables as mean and standard deviation. The association between categorical variables was tested using the Chi-Square test. $P<0.05$ was considered statistically significant. Other statistical tests used were the Mann-Whitney U test and Pearson's Correlation.

Results

Table 1

		Hypothyroid Myopathy		To tal	χ 2	df	p
		Present	Absent				
Hypertension	Present	49	14	63	6.133	1	0.013
	Absent	20	17	37			
Dyslipidemia	Present	20	4	24	3.033	1	0.082
	Absent	49	27	76			
Comorbidities and myopathy in the study population							
Symptomatology		**Hypothyroid Myopathy**			**χ 2**	**df**	**p**
		Present	**Absent**				
Easy fatigability	Present	57	23		0.947	1	0.331
	Absent	12	8				
Increased sensitivity to cold	Present	43	6		15.8	1	<0.001
	Absent	26	25				
Depression	Present	39	8		8.101	1	0.004
	Absent	30	23				
Anorexia	Present	33	10		2.115	1	0.146
	Absent	36	21				
Weight gain	Present	21	5		2.275	1	0.131
	Absent	48	26				
Constipation	Present	26	14		0.499	1	0.480
	Absent	43	17				
Impaired memory	Present	1	1		0.334	1	0.557
	Absent	68	30				
Symptoms of hypothyroidism and myopathy							
		Hypothyroid Myopathy			**χ 2**	**df**	**P**
		Present	**Absent**				
Swelling of limbs/face	Present	25	15		1.317	1	0.251
	Absent	44	16				
Sluggish ankle jerk	Present	12	3		0.998	1	0.318
	Absent	57	28				
Dry/Coarse skin	Present	8	2		0.629	1	0.428
	Absent	61	29				
Hoarseness of voice	Present	10	8		1.855	1	0.173
	Absent	59	23				
Goitre	Present	11	1		3.275	1	0.070
	Absent	58	30				
Bradycardia	Present	5	0		2.365	1	0.124
	Absent	64	31				
Macroglossia	Present	2	2		0.703	1	0.402
	Absent	67	29				
Periorbital puffiness	Present	20	9		<0.001	1	0.996
	Absent	49	22				
Non pitting edema(Myxedema)	Present	23	12		0.272	1	0.602
	Absent	46	19				
Signs of Hypothyroidism and Myopathy							

Among the comorbidities studied, hypertension had a statistically significant relation with hypothyroid myopathy (p=0.013).

There exists a statistically significant relationship between increased sensitivity to cold (p<0.001) and depression (p=0.004) to hypothyroid myopathy when compared to other symptoms of hypothyroidism. Easy fatigability, anorexia, weight gain, constipation and impaired memory were the other symptoms considered in the study.

There exists no statistically significant relationship between any of the hypothyroid signs with respect to hypothyroid myopathy.

Table 2

Hypothyroid Myopathy	Lower limb	Upper Limb	None	Total	χ 2	df	p
Present	9	60	0	69	95.792	2	<0.001
Absent	1	0	30	31			
Total	10	60	30	100			

Limb predominance in hypothyroid myopathy

	Hypothyroid Myopathy	N	Mean	Std. Deviation	Std. Error Mean	Mean Rank	Sum of Ranks	U	p
TSH	Present	69	18.88	11.237	1.352	57.14	3943.00	611.0	0.001
	Absent	31	13.35	3.123	0.561	35.71	1107.00		

Serum TSH levels and hypothyroid myopathy

	Hypothyroid Myopathy	N	Mean	Std. Deviation	Std. Error Mean	Mean Rank	Sum of Ranks	U	p
CPK	Present	69	883.58	731.496	88.062	64.22	4431.50	122.5	<0.001
	Absent	31	117.42	89.208	16.022	19.95	618.50		

Serum CPK levels and hypothyroid myopathy

There exists a statistically significant relationship between upper limb weakness and hypothyroid myopathy (p<0.001). Proximal myopathy can be considered a classical symptom of patients with hypothyroid myopathy. Since the values of biochemical parameters studied didn't follow a normal distribution, the statistical test used for analysis was the Mann-Whitney U test (non-parametric), depicted as U in the table along with the level of significance (p). The mean rank and sum of ranks was estimated for analysis. There exists a statistically significant relation between S.TSH levels and hypothyroid myopathy. (p=0.001)

Among the serum muscle enzymes studied, the most statistically significant relationship was for S. CPK (p<0.001) with hypothyroid myopathy. The mean CPK value in those with hypothyroid myopathy was 883.58 which is 7.5 times higher than that of those without hypothyroid myopathy (117.42).

Table 3

	Hypothyroid Myopathy	N	Mean	Std. Deviation	Std. Error Mean	Mean Rank	Sum of Ranks	U	p
LDH	Present	69	357.43	129.250	15.560	54.75	3778.00	776.0	0.029
	Absent	31	301.26	79.550	14.288	41.03	1272.00		

Serum LDH levels and hypothyroid myopathy

	Hypothyroid Myopathy	N	Mean	Std. Deviation	Std. Error Mean	Mean Rank	Sum of Ranks	U	p
U. MYOGLOBIN	Present	69	2.72	5.283	0.636	59.44	4101.50	452.5	<0.001
	Absent	31	0.30	0.114	0.020	30.60	948.50		
Urine myoglobin levels and hypothyroid myopathy									
	Hypothyroid Myopathy	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**Mean Rank**	**Sum of Ranks**	**U**	**p**
ANTI TPO	Present	69	254.62	328.276	39.520	57.67	3979.00	575.0	<0.001
	Absent	31	57.45	73.430	13.188	34.55	1071.00		
Serum Anti TPO levels and hypothyroid myopathy									

S. LDH values were elevated in those with hypothyroid myopathy and had got a statistical significance (P=0.029). Urine myoglobin had a statistically significant relation with hypothyroid myopathy (P<0.001). The mean value of anti-TPO in myopathic patients was 254.62 which had got a statistically significant relation with hypothyroid myopathy in the study. (P<0.001).

Table 4: Correlation Between ANTI-TPO And S. CPK

Correlations			
		CPK	ANTI TPO
CPK	Pearson Correlation	1	0.812**
	Sig. (2-tailed)		0.000
	N	100	100
Anti TPO	Pearson Correlation	0.812**	1
	Sig. (2-tailed)	0.000	
	N	100	100
**. Correlation is significant at the 0.01 level (2-tailed).			

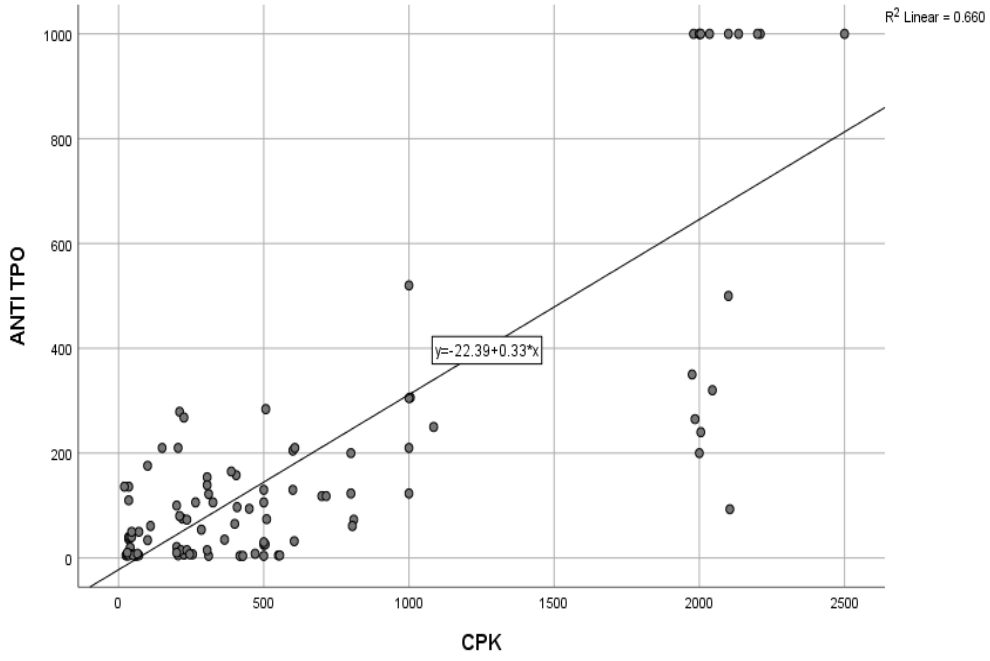

Figure 1: Scatter PLOT – Anti-TPO with CPK

ANTI-TPO and S. CPK have a statistically significant linear relationship (r=0.812, p<0.001). The direction of the relationship is positive. As ANTI-TPO increase, S.CPK values also increase. The magnitude or strength of association is strong as $R^2 = 0.660$.

Table 5: Correlation Between S. TSH and S. CPK

Correlations			
		TSH	CPK
TSH	Pearson Correlation	1	.557**
	Sig. (2-tailed)		.000
	N	100	100
CPK	Pearson Correlation	.557**	1
	Sig. (2-tailed)	.000	
	N	100	100
**. Correlation is significant at the 0.01 level (2-tailed).			

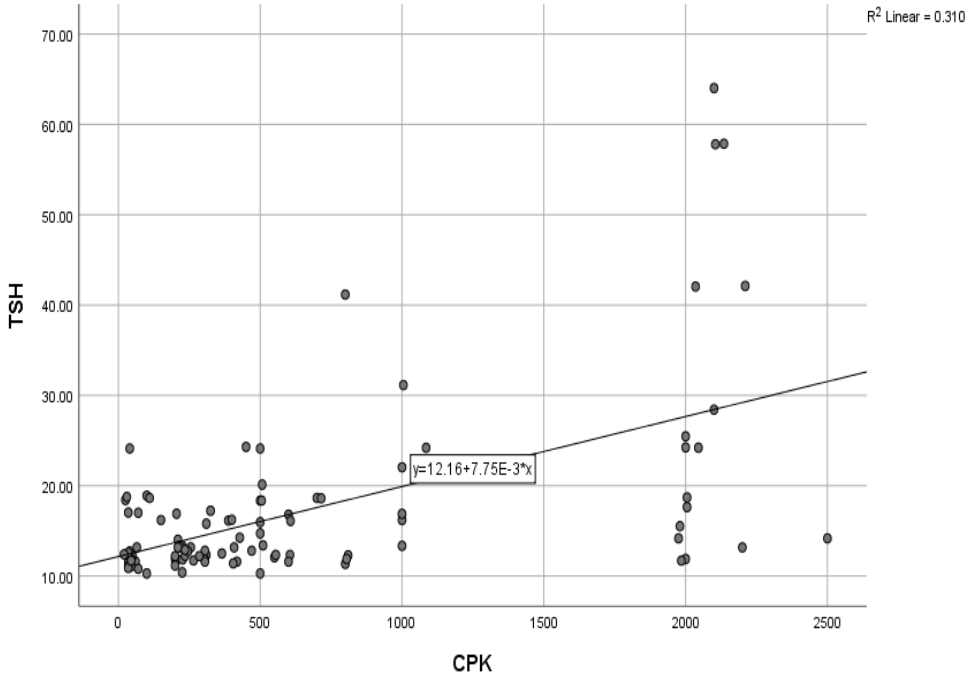

Figure 2: Scatter Plot – S. TSH with CPK

S. TSH and S. CPK have a statistically significant linear relationship (r=0.557, p<0.001). The direction of the relationship is positive. As S.TSH increase, S.CPK values also increase. The magnitude or strength of the association is strong as $R^2 = 0.310$

Discussion

Out of the 100 patients enrolled in the study, the majority (39%) were in the age group 51-60 years followed by 30% in the age group 31-40. There is no statistically significant relation for hypothyroid myopathy in any age group (p 0.073) comparable to a previous study by Astrom et al. [13] Among the 100 patients enrolled in the study, 76 were females and 24 were males. Hence the proportion of hypothyroid subjects with myopathic symptoms is predominantly females. These findings were comparable to the previous study by Fariduddin and Bansal. [14]

While assessing the comorbidities of the subjects, hypertension has got a statistically significant relation with hypothyroid myopathy (p=0.013). But Anandhasayanam et al [15] found that

dyslipidemia was the major comorbidity associated with hypertension. Alcoholism, smoking, and other habits have no statistical significance with respect to hypothyroid myopathy in the study.

While analysing the presenting symptoms of hypothyroidism, the most common symptoms are easy fatigability, increased sensitivity to colds, depression and weight gain. This is comparable to a previous study by El-Shafie [16] where all these symptoms of hypothyroidism were noted and there was no statistical relation for any of the symptoms. In contrast to these observations by El-Shafie, [16] in this study there exists a statistically significant relationship between increased sensitivity to cold ($p<0.001$) and depression ($p=0.004$) to hypothyroid myopathy when compared to other symptoms of hypothyroidism.

Clinical signs of hypothyroidism were studied and most of the patients didn't have any of the expected signs like dry/coarse skin, hoarseness of voice, goitre, bradycardia, macroglossia, periorbital puffiness and myxedema. These findings were comparable to Gaitan and Cooper's. [17]

On analysing the clinical profile of hypothyroid myopathy, there is no statistically significant age predilection for muscle symptoms in patients with hypothyroidism according to the study. This finding is comparable to Fariduddin and Bansal. [13] Most patients had muscle aches and pains along with stiffness rather than any of these alone. Joint symptoms were less predominant in patients with hypothyroid myopathy as per the study. A similar observation is also described by Golding. [18] It is worth mentioning that on observing the pattern of myopathy, Proximal "Limb-Girdle" weakness of upper limbs is much more common in hypothyroid myopathy as per the study ($p<0.001$). This finding is comparable to Barohn et al, [2] who also stated that the distal muscles are usually involved, but to a much lesser extent. This pattern of weakness is seen in most hereditary and acquired myopathies and therefore, is the least specific in arriving at a particular diagnosis.

About 40% of the study population was overweight and 31% were obese. This accounts for 71% of the study population. The study shows a statistically significant relation between S. TSH levels with the BMI of the patients ($p<0.001$). This finding is comparable to the study by Sanyal and Ray Chaudhuri. [19]

Laboratory parameters were done in the study subjects to confirm overt hypothyroidism with S. TSH and FT4 levels. Serum muscle markers done included S. CPK, S. LDH and SGOT. In addition, myoglobin levels in the urine sample are estimated to assess the presence of myoglobinuria in patients with hypothyroid myopathy. Also, ANTI-TPO levels were estimated to assess the prevalence of autoimmune thyroid illness among the subjects. A statistically significant relationship was noted between S. TSH levels and hypothyroid myopathy in the study ($p=0.001$). S. TSH and S. CPK have a statistically significant linear relationship ($r=0.557$, $P<0.001$). The direction of the relationship is positive. As S.TSH increase, S.CPK values also increase. The magnitude or strength of association is strong as $R2 = 0.310$. This observation is comparable to McKeran et al, [20] who proved the same relation by performing muscle biopsies before and after treatment with L-Thyroxine in hypothyroid myopathy patients. FT4 has no statistically significant relationship for those with hypothyroid myopathy. Among the serum muscle enzymes studied, there exists a statistically significant relation between S. CPK ($p<0.001$) and S. LDH ($p=0.029$) with hypothyroid myopathy. These findings are comparable to a previous study by Giampietro et al. [21] SGOT has no statistically significant relationship for those with hypothyroid

myopathy in the study. Urine myoglobin has a statistically significant relation with hypothyroid myopathy ($p<0.001$). This observation is comparable to Nikolaidou et al, [22] in which they substantiate rhabdomyolysis secondary to Hashimoto's thyroiditis resulting in hypothyroidism and myopathy thereby elevating S. CPK and urine myoglobin.

There is a statistically significant relation between anti-TPO and hypothyroid myopathy in the study ($p<0.001$). It is comparable to the study by Rodolico et al, [23] where patients referred with complaints of muscular fatigability, myalgia, cramps, or proximal weakness were followed up. Laboratory investigations showed that all patients had hypothyroidism due to Hashimoto's thyroiditis (atrophic variant in 9/10). Classic symptoms/signs of hypothyroidism such as lethargy, constipation, cold intolerance, myxedematous facies, and/or bradycardia were absent. Muscular complaints improved greatly and then disappeared after substitutive levothyroxine treatment.

ANTI-TPO and S. CPK have a statistically significant linear relationship ($r=0.812$, $p<0.001$) in the study. The direction of the relationship is positive. As ANTI-TPO increase, S.CPK values also increase. The magnitude or strength of association is strong as $R^2 = 0.660$. This observation is comparable to Leonardi et al. [24]

Conclusion

Increased sensitivity to cold and depression are the two common symptoms present in hypothyroid myopathy. Proximal “Limb-Girdle” pattern weakness of upper limbs is much more common in hypothyroid myopathy. Serum TSH levels and Serum muscle enzymes CPK, LDH, and urine myoglobin have a significant relationship with hypothyroid myopathy.

Anti-TPO has a significant relationship with hypothyroid myopathy, strongly suggesting an autoimmune aetiology. Anti-TPO has a significant positive linear relationship with CPK values, hence imparting the need for testing it in hypothyroid patients with symptoms of myopathy.

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