CME CREDIT **EDUCATIONAL OBJECTIVE:** Readers will take a systematic approach to evaluating asymptomatic creatine kinase elevation

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Approach to asymptomatic creatine kinase elevation

ABSTRACT

How to manage a patient who has an elevated serum creatine kinase (CK) level but no or insignificant muscle-related signs and symptoms is a clinical conundrum. The authors provide a systematic approach, including repeat testing after a period of rest, defining higher thresholds over which pursuing a diagnosis is worthwhile, and evaluating for a variety of nonneuromuscular causes. They also outline a workup for neuromuscular causes.

KEY POINTS

Standard reference ranges for serum CK levels used by most laboratories are too low and lead to overdiagnosis of abnormal values.

Serum CK levels are strongly affected by race, sex, and physical activity.

A patient with truly elevated levels should be evaluated for a variety of nonneuromuscular causes, including endocrine disorders, metabolic disturbances, drug effects, and malignancy.

Neuromuscular causes should be investigated only after ruling out nonneuromuscular causes and after considering whether potential benefits of a diagnosis outweigh the risks and expense of extensive testing.

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Measuring serum creatine kinase (CK) is an important part of the evaluation of patients with muscle weakness or myalgia, and of assessing patients with myopathies or rhabdomyolysis. But elevated CK sometimes is an incidental finding in a patient without muscle-related symptoms or with only minimal nonspecific muscle symptoms (eg, cramps, spasms, fatigue) that do not significantly interfere with activities of daily living. This condition is sometimes referred to as "asymptomatic hyper-CK-emia." Four other muscle enzymes that may also be elevated are aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and aldolase.

This review focuses on the evaluation of patients with elevated CK without significant muscle-related symptoms and proposes an algorithm for this purpose (**Figure 1**).

CURRENT THRESHOLDS MAY BE LOW

What appears to be an elevated CK level may in fact be normal, and it is important to determine in the initial assessment whether a CK value is truly abnormal.

Most laboratories use the central 95% of observations in white people as a reference range for serum CK, assuming that levels have a gaussian (bell-shaped) distribution, which is usually about 0 to 200 IU/L. Using these parameters, an abnormal CK level was observed in 19% of men and 5% of women in a study of nearly 1,000 healthy young people,[1] leading to overdiagnosis.

The actual distribution of serum CK levels in a healthy population is markedly skewed toward higher values and is nongaussian.[1–3] A 97.5% normal threshold is associated with a much lower false-positive rate and is recom-

Elevated creatine kinase (CK)
and no muscle symptoms
and normal muscle examination

↓

Repeat CK measurement after 7 days, avoiding exercise in the interval → **If normal, stop**

↓

CK level > 1.5 times the upper limit of normal for sex and race, ie: → **If not, stop and observe**
> 1,200 IU/L in a black man
> 621 IU/L in a black woman
> 504 IU/L in a white man
> 325 IU/L in a white woman

↓

Rule out nonneuromuscular causes (see **Table 1**), such as: → **If present, treat**
Endocrine disorders
Connective tissue diseases
Cardiac and renal diseases
Viral illness
Pregnancy
Celiac disease
Medications
Metabolic diseases
Surgery
Malignancy
Macro CK

↓

Discuss with patient the limited utility of further workup

↓

Electromyography and muscle biopsy

↓ **If normal, "idiopathic hyper-CK-emia"**

↘ **If abnormal, pursue workup of neuromuscular causes** such as:
Dystrophies
Metabolic conditions
Congenital conditions
Inflammatory conditions

FIGURE 1. Diagnostic workup of asymptomatic creatine kinase elevation.

mended by the European Federation of Neurological Societies (now the European Academy of Neurology).[4] This group also recommends pursuing further investigation only for patients whose level is at least 1.5 times the upper limit of normal; this threshold results in only a small reduction in sensitivity.

CK levels vary significantly by sex and race.[5] Possible reasons include differences in muscle mass or total body mass and inherited differences in the permeability of the sarcolemma to CK.[6] There is also a small reduction in CK levels as people age.[2]

The European Federation of Neurological Societies suggests redefining elevated CK as values 1.5 times beyond the upper limit of normal. Based on a 97.5% threshold and normal values determined by Brewster et al[3] for black and white men and women, the following thresholds can be used to help decide whether to pursue further evaluation[4]:

- White women—325 IU/L
- White men—504 IU/L
- Black women—621 IU/L
- Black men—1,200 IU/L.

PHYSICAL ACTIVITY RAISES CK

CK levels transiently rise after exercise or heavy manual labor. Serum CK levels may increase to as much as 30 times the upper limit of normal within 24 hours of strenuous physical activity, then slowly decline over the next 7 days. The degree of CK elevation depends on the type and duration of exercise, with greater elevation in those who are untrained.[2,4]

In assessing asymptomatic or minimally symptomatic CK elevation, the test should be repeated after 7 days without exercise. A large community study in Norway found that repeat CK levels in people with incidentally discovered elevated CK were normal after 3 days of rest in 70% of cases.[2]

NONNEUROMUSCULAR CAUSES NEED TO BE INVESTIGATED

Asymptomatic or minimally symptomatic elevated CK can be due to a primary neuromuscular disease or a variety of nonneuromuscular causes.

Patients who still have elevated CK after taking into account the 97.5% threshold, repeat testing after a week of rest, and a level more than 1.5 times the upper limit of normal for sex and race should first be evaluated for the many nonneuromuscular conditions that can cause elevated CK (**Table 1**).[7–9]

Cardiac causes should be evaluated by history and physical examination, electrocardiography, and possibly testing for cardiac troponins.

Drugs commonly elevate CK

Prescription drugs and supplements are an important and common cause of CK elevation, so it is important to carefully review medications the patient is taking.

Statins can cause myalgia, muscle weakness, and rhabdomyolysis. Up to 5% of users develop CK elevation, typically 2 to 10 times the upper limit of normal.[10] CK usually drops after stopping statins but may require weeks to months to normalize. Rarely, statin users develop a serious immune-mediated necrotizing myopathy.[11–13]

The diversity of response to statin therapy appears to have a genetic basis. The SEARCH Collaborative Group[14] conducted a genome-wide association study of 300,000 markers in 85 patients with definite or incipient myopathy and in 90 controls, all of whom were taking simvastatin 80 mg daily. They identified a single-nucleotide polymorphism in the *SLCO1B1* gene on chromosome 12 that was strongly associated with a higher risk of statin-induced myopathy.

Patients with statin-related myopathy seem to have a higher frequency of occult metabolic muscle disease than the general population, also suggesting genetic susceptibility, although ascertainment bias could be a factor.[14]

Mechanisms of CK elevation in response to statins include increased muscle membrane fragility due to decreased cholesterol content, inhibition of isoprenoid production (a necessary step in the synthesis of membrane proteins), and depletion of ubiquinone, leading to mitochondrial dysfunction.

Macro CK: An abnormal enzyme complex

About 4% of patients with asymptomatic or minimally symptomatic elevated CK have "macro CK," an enzyme complex with an atypically high molecular mass and reduced clearance, resulting in abnormally high blood levels of CK. Macro CK type 1 is more common and is found in up to 1.2% of the general population: complexes are composed of CK and immunoglobulin and are associated with autoimmune diseases.[9,15] Macro CK type 2 complexes consist of CK and an undetermined protein and are associated with malignancies.

CK electrophoresis is required to detect macro CK. Types 1 and 2 can be distinguished by protein G affinity chromatography.[9,15]

TABLE 1

Nonneuromuscular disorders that can cause elevated creatine kinase

Endocrine disorders
Hyperthyroidism (rare)
Hypothyroidism
Hyperparathyroidism
Acromegaly
Cushing syndrome

Metabolic disturbances
Hyponatremia
Hypokalemia
Hypophosphatemia

Muscle trauma
Strenuous exercise
Intramuscular injections
Needle electromyography
Seizures

Medications
Statins
Fibrates
Antiretrovirals
Beta-blockers
Clozapine
Angiotensin II receptor blockers
Hydroxychloroquine
Isotretinoin
Colchicine

Others
Celiac disease
Malignancy
Macro CK
Surgery
Pregnancy
Cardiac disease
Acute kidney disease
Viral illness
Predisposition to malignant hyperthermia

Endocrine disorders

Muscle involvement in endocrine disorders often presents with muscle weakness in addition to muscle enzyme abnormalities.

Hypothyroidism often causes weakness, cramps, myalgia, and a mild to moderate serum CK elevation.[16] Severe CK elevation has been reported to occur after vigorous exercise.[17] Thyroid replacement usually results in normalization of serum CK levels in 1 to 2 months.[18]

Elevated CK is sometimes an incidental finding

TABLE 2

Occult or latent neuromuscular disorders causing elevated creatine kinase

Muscle dystrophies
Duchenne and Becker muscular dystrophies
Dystrophin mutations in female carriers
Limb girdle
Myofibrillar myopathy
Desmin-related myofibrillar myopathy
Myotonic dystrophy

Metabolic and mitochondrial disorders of muscle
Carnitine palmitoyltransferase II deficiency
McArdle disease
Myoadenylate deaminase deficiency
Mitochondrial myopathies
Pompe disease (acid maltase deficiency)

Inflammatory myopathies
Hypomyopathic dermatomyositis
Inclusion body myositis
Clinically amyopathic dermatomyositis
Antisynthetase syndrome

Others
Familial elevated creatine kinase
Sarcoid myopathy
Motor neuron diseases
Charcot-Marie-Tooth disease
Other congenital diseases

Hyperthyroidism is typically associated with normal serum CK concentrations, but in rare cases it can cause rhabdomyolysis.[19]

NEUROMUSCULAR CAUSES ARE NOT ALWAYS WORTH PURSUING

Only after the nonneuromuscular causes of elevated CK have been ruled out should neuromuscular disorders be considered (**Table 2**). Evaluation with electromyography, nerve conduction studies, and muscle biopsy may lead to the diagnosis of a specific neuromuscular disorder: patients may be in the presymptomatic stage of disease and may or may not eventually develop muscle weakness or other symptoms.[20,21]

Is testing needed?

Most adult dystrophies and metabolic myopathies have no available treatment and their course is often benign, particularly if they present only with asymptomatic elevated CK. The value of a potentially extensive, expensive, and invasive evaluation for a specific neuromuscular cause should be weighed against the limited yield and treatment options. Moreover, specialized testing such as biochemical muscle enzyme analysis, sarcolemmal protein staining, and genetic testing are not available at all centers.

The European Federation of Neurological Societies guidelines recommend biopsy for patients with asymptomatic elevated CK who also have any of the following:

- Abnormal (myopathic) findings on electromyography
- CK more than three times the upper limit of normal
- Age less than 25
- Exercise intolerance.[4]

Idiopathic inflammatory myopathies rarely present with asymptomatic elevated CK.[22–26] In one study,[27] they were found in just 5% of patients with asymptomatic elevated CK.

Hypomyopathic dermatomyositis and **inclusion body myositis** can present with mild CK elevations with normal muscle strength, especially early in the disease course. A myositis subset of **antisynthetase syndrome** can present with mildly elevated CK and interstitial lung disease.[27] Many of the inflammatory myopathies respond to treatment so are worth investigating.

In view of complexities in diagnosis of these conditions, one should proceed with testing only after discussing it with patients. Referral to a rheumatology specialist is preferred.

MUSCLE BIOPSY, ELECTROMYOGRAPHY, AND NERVE CONDUCTION STUDIES

Electromyography, nerve conduction studies, or muscle biopsy, or a combination of these tests, is usually needed to investigate neuromuscular causes of elevated CK.

Muscle biopsy abnormalities are found in about two-thirds of cases of asymptomatic elevated CK, but most abnormalities include nonspecific myopathic changes that are not diagnostic. A muscle biopsy that may include special stains for sarcolemmal proteins for muscular dystrophy and biochemical muscle enzyme analysis for metabolic myopathies is diagnostic in only 20% to 25% cases of asymptomatic elevated CK on average, with a variation between different series of 0% to 79%.[7,21,27–33]

Electromyography and nerve conduction studies alone add little to the workup of asymptomatic elevated CK apart from a modest negative predictive value and as a guide for muscle biopsy. For a very few neuromuscular disorders causing an elevated CK (eg, motor neuron disease, Charcot-Marie-Tooth disease, myotonic dystrophy), electromyography and nerve conduction studies could suffice to make the diagnosis.

Electromyography and nerve conduction studies detect abnormalities in nearly half of cases of asymptomatic CK elevation,[7,21,27,28,30,31,33] but, as with biopsy, most changes are nonspecific. Although electromyography and nerve conduction studies can help distinguish primary neuropathic from myopathic disorders, the sensitivity and specificity are low for diagnosis. Normal studies do not rule out a condition, and abnormal studies are not diagnostic of a particular condition, although completely normal studies provide strong evidence against a severe neuromuscular disorder.

Combined testing

Using combined muscle biopsy, electromyography, and nerve conduction studies, the likelihood of making a diagnosis in patients with asymptomatic elevated CK is 28% on average (range of studies 4%–79%),[2,7,21,26–28,30–32] and findings are nonspecific in 30% to 40% of cases. Findings are normal in about 30% to 40% of cases, which are thus diagnosed as idiopathic asymptomatic elevated CK.[28–31,34]

Prelle et al[31] retrospectively reviewed the cases of 114 patients, ages 3 to 70, with incidentally discovered elevated CK and few or no symptoms, who underwent muscle biopsy, electromyography, and nerve conduction studies after nonneuromuscular causes were ruled out. Although muscle biopsy findings were abnormal in 39% of cases, a diagnosis was established in only 18% of cases after an extensive workup: the diagnosis was definitive in only 10% and included dystrophinopathies, metabolic myopathies, and rare noninflammatory myopathies. For the remaining 8%, the diagnosis was probable and included four cases of partial carnitine palmitoyl transferase deficiency, three cases of malignant hyperthermia, and two rare inherited disorders.

DNA testing

In women with a serum CK less than three times the upper limit of normal who have a family history of Duchenne or Becker muscular dystrophy, DNA analysis of blood lymphocytes identifies 70% of carriers.[4]

IDIOPATHIC ELEVATED SERUM CK

Rowland et al[35] first coined the term "idiopathic hyper-CK-emia" and defined it as persistent elevation of serum CK despite a normal neurologic examination and testing, including electromyography, nerve conduction studies, and muscle biopsy.[35,36] To receive this diagnosis, patients must also have no family history or clinical evidence of neuromuscular disease.

Idiopathic elevated serum CK is sometimes familial. In one study,[37] elevated CK was found in family members of 13 of 28 unrelated probands. In the 13 families, 41 individuals had elevated CK. Genetic studies revealed that the condition is genetically heterogeneous and autosomal dominant in at least 60% of cases, with higher penetrance in men.

D'Adda et al[26] followed 55 people with idiopathic elevated CK for 7 years. Ten percent were eventually diagnosed with a neuromuscular disorder, 10% developed malignancy, and the remaining 80% developed no new condition. The CK level normalized or decreased in many patients, but most continued to have persistent CK elevations with minimal or no symptoms.

Most abnormal findings on biopsy, electromyography, and nerve conduction studies are nonspecific

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