Subnormal activity of creatine kinase (CK, ATP: creatine N-phosphotransferase, EC 2.7.3.2) in serum has been observed in a variety of clinical conditions. Subnormal activity may be found as a consequence of diminished efflux of the muscle enzyme into serum from reduced physical activity caused by illness or advanced age or may result from reduced muscle mass accompanying muscle wasting or cachectic states. Low serum CK values reported in acute viral hepatitis have been explained on the basis of reduced physical activity because these patients have been confined to bed for therapeutic reasons or because of the severity of the illness (1). Low CK activities in patients with alcoholic liver disease (2) have been considered to reflect the reduced muscle mass commonly observed in alcoholics. Reduced serum CK activity has also been observed in patients with connective tissue disease unassociated with diminished physical activity (3), but the cause of this is obscure. Diminished enzyme efflux from altered muscle membrane permeability may account for the low serum CK values reported in Cushing’s disease or found in patients on steroid therapy (4) and in thyrotoxicosis. A similar mechanism may be responsible for low serum CK in patients receiving estrogen therapy, estrogen-containing contraceptives, or tamoxifen (5).

An inverse correlation between (high) plasma alkaline phosphatase and (low) CK activities has been reported (6) but is unconfirmed (7). It had been postulated that the low CK values result from phosphatase hydrolysis of phosphate substrates in the CK assay. Low serum CK values have also been observed with macromolecular complex formation that is caused by enzyme-binding immunoglobulins, with inhibition of the enzyme activity from isteric hindrance.

Low CK activity has been reported in malignant disease metastatic to liver (8). This was accompanied by a prolonged lag phase in the course of the enzyme determination, which was eliminated by preincubation of the serum with thiol. Even immediately after blood sampling, CK in serum may be inappropriately low because of reversible inactivation of enzyme thiol groups (9). This may be a consequence of release of the enzyme in a partly inactivated form or from CK inactivation within the circulation. Similarly, therapy with the antihypertensive drug captopril has been observed to produce low serum CK activity (10), possibly because of inhibition from disulfide metabolism formation.

Delanghe et al. (11) found low serum CK activity in intensive care patients, the majority of whom had severe infections or septicemia; the low activity reversed with clinical improvement of the patients. This finding was not thought to be a result of decreased cell permeability to the enzyme because other enzymes of cytoplasmic origin were not decreased in serum. In this issue, Gunst et al. (12) extend these previous observations. They examined CK activity and glutathione concentrations in serum from 200 healthy subjects and a series of 38 patients with multiple organ failure, muscle wasting, and low serum CK. Overall, low serum glutathione concentrations correlated with low serum CK, and in the organ failure group, low serum CK was accompanied by very low serum glutathione concentrations. They noted that low serum CK in the circulation associated with glutathione depletion could not be restored by thiol-reducing compounds in the CK assay. Endogenous glutathione can be regarded, therefore, as a CK-preserving agent during the stay of the enzyme in the circulation. Their patients, as judged by increased serum myoglobin and aldolase activity, had evidence of muscle injury. They therefore recommended that (low) CK activity should be interpreted with caution in patients with liver disorders and multiple organ failure suspected of muscle injury. Myoglobin and aldolase are not ideal markers of such injury, because the former may be increased from renal failure and the latter from liver disease. Nor do increased serum concentrations generally differentiate between skeletal and cardiac muscle damage. Fortunately, newer markers such as serum carbonic anhydrase III can identify the former, and markers such as cardiac troponins can identify the latter.

The Gent group has done a service in identifying yet another cause of inappropriately subnormal serum creatine kinase activity. Awareness of the various causes and the application of newer tests of cardiac and skeletal muscle damage should avoid these diagnoses being missed.

References

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