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The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will **not** issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: **MT00025**.

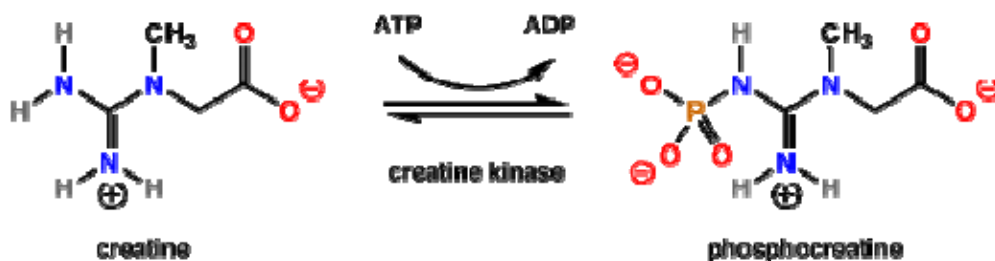
Each attendee should claim **THREE** CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

## CHEMISTRY LEGEND

August 2009

### Creatine kinase (CK)

**Creatine kinase (CK)**, also known as Creatine phosphokinase (CPK) or phospho-creatine kinase or sometimes wrongfully also creatinine kinase, is an enzyme expressed by various tissues and cell types. CK catalyses the conversion of Creatine and consumes adenosine triphosphate (ATP) to create phospho-creatine (PCr) and adenosine diphosphate (ADP). This CK enzyme reaction is reversible, such that also ATP can be generated from PCr and ADP.



In tissues and cells that consume ATP rapidly, especially skeletal muscle, but also brain, photoreceptor cells of the retina, hair cells of the inner ear, spermatozoa and smooth muscle, phospho-creatine serves as an energy reservoir for the rapid buffering and regeneration of ATP in situ, as well as for intracellular energy transport by the phospho-creatine shuttle or circuit. Thus Creatine kinase is an important enzyme in such tissues.

Clinically, Creatine kinase is assayed in blood tests as a marker of myocardial infarction (heart attack), rhabdomyolysis (severe muscle breakdown), muscular dystrophy, and in acute renal failure.

### Types

In the cells, the "cytosolic" CK enzymes, consists of two subunits, which can be either B (brain type) or M (muscle type). There are, therefore, three different isoenzymes: CK-MM, CK-BB and CK-MB. In addition to those three cytosolic CK isoforms, there are two mitochondrial Creatine kinase isoenzymes, the ubiquitous and sarcomeric form. While mitochondrial Creatine kinase is

directly involved in formation of phospho-creatine from mitochondrial ATP, cytosolic CK regenerate ATP from ADP, using PCr. This happens at intracellular sites where ATP is used in the cell, with CK acting as an in situ ATP regenerator.

gene	protein
CKB	creatine kinase, brain, BB-CK
CKBE	creatine kinase, ectopic expression
CKM	creatine kinase, muscle, MM-CK
CKMT1A, CKMT1B	creatine kinase mitochondrial 1; ubiquitous mtCK; or <sub>u</sub> mtCK
CKMT2	creatine kinase mitochondrial 2; sarcomeric mtCK; or <sub>s</sub> mtCK

Isoenzyme patterns differ in tissues. CK-BB occurs mainly in brain tissue, and its levels rarely has any significance in the bloodstream. CK-BB expressed also in all tissues at low levels has little clinical relevance. Skeletal muscle expresses CK-MM (98%) and low levels of CK-MB (1%). The myocardium (heart muscle), in contrast, expresses CK-MM at 70% and CK-MB at 25-30%.

CK is one of the "cardiac" enzymes and is used mainly for the diagnosis and evaluation of myocardial infarction. However before a diagnosis of acute myocardial infarction can be made, two of the following 3 criteria must be met. (WHO 1971 - 1972):

1. A history of chest pain consistent with myocardial ischaemia
2. ECG changes consistent with myocardial infarction
3. Typical myocardial infarction plasma enzyme changes e.g. total CK twice the upper reference limit or increased to at least three times the initial value

### Common causes of increased plasma CK activity

Cardiac muscle	Skeletal muscle	Miscellaneous
Myocardial infarction	Muscular dystrophy	Hypothyroidism
Myocarditis	Myoglobinuria	Cerebrovascular accidents
	Dermatomyositis	Hyper/hypothermia
	Generalized convulsions	Diabetic ketoacidosis
	Severe exercise	Septicaemia
	Muscle trauma	Malignancy
	Myopathy: alcoholic	Immunoglobulin-CK complexes
	Intramuscular injection	

The majority of these disorders are usually evident clinically and generally there is no problem determining the cause of the high enzyme level. However, there are two situations where further investigations may be necessary to determine the tissue of origin:

1. A patient with a raised plasma CK due to non-cardiac diseases (e.g. skeletal muscle damage), who has chest pain and in whom the ECG is unhelpful in diagnosis.
2. A patient with an isolated elevated CK level in whom the cause is not obvious clinically.

In the first situation the problem can usually be resolved by measuring the CK isoenzymes. However there are two important points to bear in mind when interpreting CK isoenzyme measurements:

1. Cardiac muscle consists mainly of CK-MM and less than 15% of CK-MB; skeletal muscle is mostly CK-MM but contains 1% CK-MB. Thus, very high levels of plasma CK activity due to skeletal muscle damage will show quite high absolute levels CK-MB, but the proportion of CK-MB will still be less than 1-2%.
2. There are a number of diseases, unrelated to cardiac or skeletal muscle, which can be associated with high plasma levels of CK-MB; e.g. malignancy, septicaemia. In such cases the increased plasma CK may represent an immunoglobulin-CK complex.

### Case Study

A 61 year old woman presented with back and chest pain for investigation. She had three episodes of central stabbing chest pain over the past year. The pain did not radiate down her arms and was thought to be atypical for myocardial ischaemia. Her medication on admission included clofibrate for hypercholesterolaemia. On examination she revealed a slow manner and speech, and a short unsteady gait. Her blood pressure was 150/90 and pulse rate 70. Her plasma electrolyte values and liver function tests were normal, but she had abnormally high plasma CK and LD activities:

Plasma CK	6098 U/L	(30 - 140)
Plasma LDH	654 U/L	(85 - 180)

### Differential Diagnosis

The history of chest pain and hypercholesterolaemia, coupled with high plasma CK, suggested the possibility of cardiac disease and she was given a provisional diagnosis of myocardial infarction.

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### References

1. Cases in chemical pathology - A Diagnostic approach 4<sup>th</sup> edition
2. Fundamentals of Clinical Chemistry 3<sup>rd</sup> edition - NW Tietz

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### Questions

1. Discuss the different types of CK enzymes and isoenzymes.
  2. According to WHO, what criteria must first be met before a diagnosis of Myocardial infarction can be made?
  3. Discuss the common causes of an increased plasma CK activity?
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