

Macro creatine kinase*

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Macro creatine kinase (Macro CK), a macro enzyme, is a major cause of misdiagnosis of myocardial infarction upon determination of total creatine kinase and creatine kinase isoenzyme levels. It presents in elderly female patients with an approximate prevalence of 1 %. Based on composition, there are two major types of macro CK Type 1 macro CK is a complex of Type 1 being an immune complex of creatine kinase with many types of immunoglobulins. Type 1 creatine kinase has been noted for its correlation with autoimmune diseases, especially the myositis group. Type 2 macro CK is a mitochondrion-derived macro CK present in malignancy, especially small cell lung cancer, gastrointestinal cancer and colorectal cancer. The presence of macro CK type 2 is a poor prognostic sign in patients with malignancy.

Key word : Macro creatine kinase.

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Objective

1. To inform the readers about the macro creatine kinase.

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Macro creatine kinase เป็นแมคโครเอนไซม์ที่ก่อให้เกิดความผิดพลาดในการวินิจฉัยโรคกล้ามเนื้อหัวใจตายจากการขาดเลือด ในการตรวจวัดระดับ *creatin kinase* โดยรวมและ *isoenzyme* พิจารณาตามองค์ประกอบจะแยก *Macro creatine kinase* ได้ 2 ชนิด คือชนิดที่ 1 เกิดจากสารประกอบเชิงซ้อนของสารภูมิต้านกับเอนไซม์ *creatin kinase* ส่วนชนิดที่ 2 เกิดจาก *mitochondria* ซึ่งมักพบร่วมกับมะเร็งปอดชนิดเซลล์เล็ก มะเร็งของระบบทางเดินอาหาร และมะเร็งของลำไส้ใหญ่และทวารหนัก การตรวจพบ *macro creatine kinase* ชนิดที่ 2 นี้บ่งบอกถึงการพยากรณ์โรคที่ไม่ดี

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

General Information about macro creatine kinase

Macro creatine kinase (Macro CK) is a major cause of elevations of the creatine kinase MB isoenzyme (CK), which may cause errors in the evaluation of patients suspected of ischemic cardiopathy.⁽¹⁻³⁾ Its presence in serum interferes with the immunoinhibition methods normally used in emergency room laboratories causing false positive results in the evaluation of the total creatine kinase level (CK), compared to the CK-MB levels. Sometimes the CK-MB activity exceeds total CK activity by more than 25%.⁽³⁻⁵⁾ Increasing concentrations of various types of creatine kinase isoenzymes mimic myocardial infarction or injury.⁽⁶⁾ Sometimes CK-MB activity exceeds the total CK activity.⁽⁷⁾ Probably a maximum of 1% of patients with suspected acute myocardial infarction.^(6,8-9) have macro CK in concentrations causing diagnostic errors. In clinical practice, markedly elevated levels of CK-MB, or increased levels of CK-MB in combination with CK-BB may point away from a myocardial origin and toward the existence of a malignancy. Macro CK can be detected as an

abnormal band in creatine kinase electrophoresis.

Macro CK can be distinguished as two type, type 1 and type 2.⁽¹⁰⁾ Presence of both variant CK isoenzymes may lead to diagnostic or therapeutic errors due to an altered CK:CK-MB ratio.⁽¹¹⁾ The prevalence of type 1 is 0.43 – 4.3 % and type 2 is 0.5-2.9%^(6,12) (Table 1). The serum total CK is significantly higher, and an increased CK-MB proportion is also significantly more common in patients with macro CK type 1 than in those with type 2. Macro CK types 1 and 2 are much more heat stable than CK - MB, and CK-BB, and thus, by heating samples for 20 min at 45 degrees C, the presence of thermostable macro types can be demonstrated.⁽⁸⁾ In addition, macro CK type 2 has a much higher activation energy than macro CK type 1. On average, macro CK type 2 accounts for approximately 25 % and more CK type 1 for approximately 10 % of the serum total CK.⁽⁸⁾ It has also been shown that approximately 90 % of the patients in whom macro Ck is detected survive at least for 1 year after macro CK has been found in their serum.

Table 1. Comparison between macro creatine kinase type 1 and type 2 characteristics.

Items	Type 1	Type 2
1. Structure	Complex between CK isoenzyme and Immunoglobulin	Polymeric of mitochondrial derived CK
2. Activation energy	Lower	Higher
3. Heat stability	Less	More
4. Electrophoretic pattern	Less cathodically migrating, variable due to complex's type	More cathodically migrating
5. Increase of total CK activity	More common	Less common
6. Increase of CK-MB proportion	More common	Less common
7. CK-MB exceed total CK case	Less common	More common
8. Relating abnormalities	Myositis	Cancer, neonatal asphyxia

Like other macro enzymes⁽¹³⁾ such as macromylase and macro lactate dehydrogenase, macro CK can be detected in advanced age and with malignant lesions.⁽¹⁴⁾ It can be found in diseases of many organ systems such as brain,⁽¹⁵⁾ thyroid,⁽¹⁶⁾ GI,⁽¹⁷⁻¹⁸⁾ prostate,⁽¹⁸⁾ and kidney.⁽¹⁹⁾ However, the macro CK isoenzyme in the serum of apparently healthy individuals has also reported.⁽²⁰⁻²³⁾

Interference of macro creatine kinase with detection of CK-MB

At present, CK-MB can be detected by four major methods:⁽⁹⁾ electroporesis, column chromatography, immunoinhibition and immunoprecipitation.⁽²⁴⁾ Of these four methods, electrophoresis has shown the highest accuracy in detecting CK-MB⁽²⁵⁾ and macro CK can be detected as a slow moving band. Whereas the other methods have shown false positive results due to macro CK interference.⁽²⁶⁻²⁷⁾

The immunoinhibition method, which is the method most widely used presently, has the disadvantage of the errors introduced because of contamination with CK-BB, CK-MM and macro-CK.⁽³⁾ With immunoinhibition procedures, which macro CK is often measured as CK-MB, leading to falsely elevated CK-MB, unrelated to acute myocardial infarction. Thus, CK-MB activity should be determined simultaneously with total CK activity. When a significant contribution by CK-BB is suspected, its presence should be confirmed by other methods.

To avoid the interference by macro CK, electrophoresis and specific immuno assays or immunochemiluminometric assays using monoclonal anti CK-MB antibodies have been recommended.⁽²⁷⁻²⁸⁾ Serial determination of both creatine kinase and lactate

dehydrogenase isoenzymes also greatly assist in the differential diagnosis of patients with presence of macro CK that may lead to the false conclusion of acute myocardial infarction.⁽⁸⁾

Macro creatine kinase type 1

Macro CK type 1 is a complex of the creatine kinase isoenzyme with immunoglobulin.^(1,14,29) It has been related to underlying cardiovascular pathology and occurs with high levels of the creatine kinase MB isoenzyme (normally above 50 % of the total activity of the creatine kinase). Many forms of complexes can be identified such as IgG linked to the BB fraction,^(1,30-33) IgA linked to the MM3 fraction,⁽³⁴⁻³⁵⁾ IgA linked to the BB fraction,⁽³¹⁻³⁶⁾ but IgG linked to the BB fraction is the most common form.^(6,10) In patients with creatine kinase - Ig complexes, transfer of the complex across the placenta from mother to fetus has been reported. These complexes are all thermostable and can be differentiated from the creatine kinases by a simple heat inactivation test (20 minutes, 45 degree or immunoinhibition of the M-subunits.⁽³⁷⁾

Most cases with macro CK type 1 have an autoimmune disease such as rhabdomyolysis⁽¹⁹⁾ or rheumatic disease.⁽³⁸⁾ It occurs more frequently in women above the age of 70 years,⁽³⁸⁾ and is often associated with complications of cardiovascular disease, life - threatening conditions, and poor outcome. However, no significant correlation has been obtained between findings of coronary angiography and the activity of macro CK type 1.

In case of macro CK-BB, immunoglobulin precipitation after addition of radiolabelled CK-BB suggests that most of the sera are linked to an immunoglobulin G.⁽³⁸⁾ Results obtained with papain -

and pepsin – digested IgG have suggested that the binding of CK-BB occurs in the antigen – binding region T_{ab} of IgG. The affinity constant, K_{eq} , for the binding of CK-BB to immunoglobulin has been calculated as 1.4×10^{11} L/mol.⁽⁴¹⁾

A formed complex of high relative molecular mass (Mr 320 kDa),⁽³⁴⁾ macro CK - MM3, consists of both CK-MM3 and immunoglobulin A (IgA). It is composed of two molecules of CK-MM3 combined with one molecule of IgA. As IgA does not form complexes with other subforms (CK-MM2 and CK-MM1) or CK-MB, the antigen specificity of IgA to CK-MM3 is exactly defined. The percentage of macro CK - MM3 in all adult patients has been calculated as 73 %, but it has not been detected in the sera of patients below the age of 12 months. No relationship has been observed between macro CK-MM3 and underlying disease. Macro CK-MM3 formation has been suggested to be an immunologic pathway for intravascular catabolism of CK - MM3 when its activity increases.⁽³⁴⁾

Macro creatine kinase type 2

Macro CK type 2,^(42 - 43) a cathodically migrating atypical creatine kinase isoenzyme, evidently is not of cytoplasmic origin; rather, it is a separate CK activity of human serum, characterized by its heat stability and, especially, by its increased molecular mass and high activation energy. The relative molecular mass of this form of creatine kinase in human serum is at least threefold that of the ordinary enzyme, and it is more therostable. Based on distinct activation energies, unlike normal cytoplasmic creatine kinases and IgG – linked CK – BB (macro CK type 1), this second form of macro CK (macro CK type 2) shows activation energies above 80 kJ/mol of

the substrate.

The exact composition of macro CK type 2 is still unknown, but there is good reason to believe that it is of mitochondrial origin because its characteristics have never been associated with the normal –size, dimeric cytoplasmic CK isoenzymes, but are typical for mitochondrial polymeric creatine kinase⁽²⁰⁾ isolated from human tissues. It is released after severe cell damage and usually appears in the blood in macromolecular forms (macro CK type 2), in a non-dimeric form.

Most patients showing macro CK type 2 are older than 50 years.⁽⁴⁵⁾ No association with gender has been reported. Macro CK type 2 is also predominantly found in severely ill patients of all ages, most commonly with malignancy.⁽⁴⁶⁾ The cancers that have been associated are small cell lung carcinoma,^(4,47) liver cancer,⁽⁴⁸⁻⁴⁹⁾ GI cancer⁽⁴⁹⁾ and colorectal cancer.^(50,51)

In pediatric patients, macro CK type 2 has also been detected in children with clinical evidence of myocardial damage. The presence of macro CK type 2 is an indicator of cellular necrosis; in pediatric cases with myocardial damage the associated conditions may be reversible but in adults with malignancies the presence of mitochondrial creatine kinase is associated with an extremely poor prognosis.^(8,48)

Disappearance of macro CK type 2 from the circulation after improvement of the associated disease has also been reported. Its occurrence in serum nevertheless is a sign of a serious illness with a high mortality rate but not inevitably a sign of impending death.⁽⁴⁵⁾ Furthermore, no correlation between the isoenzyme activity and the stage of cancer has been detected.^(18,51) Appearance of macro

CK type 2 has also been noted in non-malignant conditions such as liver cirrhosis and neonatal asphyxia.⁽¹³⁾

Clinical association of macro creatine kinase

A number of diseases have been reported to be correlated with the appearance of macro CK in serum. The details of these pathological conditions are described below.

A. Hepatobiliary system

Macro CK type 2 can be found in many hepatobiliary diseases, especially cirrhosis and liver cancer. The presence of type-2 macro CK is unrelated to the stage of either cirrhosis or hepatocellular carcinoma. It has poor diagnostic sensitivity for neoplastic diseases, and lacks of prognostic value both in cirrhosis and neoplastic diseases.⁽⁴⁸⁾ Therefore, serum type 2 macro CK isoenzyme is not a useful marker of severe liver diseases or neoplasia.

B. Respiratory system

Macro CK type 2 can be found in patients with lung carcinoma, especially in small cell lung carcinoma and oat cell carcinoma. Concerning these patients, elevated activities have been associated with disseminated disease but have little apparent value as a tumor marker for these disease.⁽⁴⁹⁾

Serum macro CK type 2 in asphyxiated newborn infants has also been observed.⁽¹³⁾ The presence of macro CK type 2 activity has been noted in 21.9 % of newborn infants with perinatal asphyxia or birth trauma. In these cases, a predominance in males has been observed and an association with a more severe clinical course, requiring prolonged hospitalization.

C. Gastrointestinal system

There have been many reports of the presence of macro creatine kinase type 2 in many gastrointestinal tumors. Concerning gastric carcinoma, the total CK activity to be markedly decreased in neoplastic stomach tissue.⁽¹⁷⁾ CK-BB is the predominant isoenzyme in both neoplastic and normal stomach tissues; however, the CK-BB/total CK ratio is increased in adenocarcinoma tissue. Both macro creatine kinase type 1 and type 2 have been detected in patients with gastric cancers.

Considering colorectal cancer, detection of macro CK in the serum of patients has also been reported.⁽⁵²⁾ However, no correlation between the isoenzyme activity and the stage of the cancer has been shown. Preliminary studies have suggested that the presence of macro - CK2 in serum may be an indicator of malignancy of the gastrointestinal tract and in particular, of colorectal cancer.^(17,50-51)

D. Neurological and musculoskeletal system

Macro CK is also predominant in cerebrovascular insufficiency due to arteriosclerosis.⁽⁵⁴⁾ High blood levels of macro CK in encephalopathy have been observed. Furthermore, macro CK type 1 can be observed in patients with myositis.⁽³⁹⁾ Association with the diagnosis of an autoimmune process in these patients, such as rhabdomyolysis has been noted.

E. Genitourinary system

The presence of macro CK in patients with chronic renal failure on maintenance hemodialysis⁽⁵⁶⁾ has been reported. In these cases, no clinical significance was observed.

Concerning genitourinary tumors, there has been a report of the prevalence of macro creatine

kinase amounting to 11.1 % in prostatic cancer. This study concluded that macro CK determination has little apparent value as a tumor marker for prostatic cancer.⁽¹⁸⁾

F. Cardiovascular system

Macro CK type 1 has been reported to be related to underlying cardiovascular pathology.⁽¹⁾ The prevalence of immunoglobulin-bound creatine kinase (macro CK type 1) in this scenario has been 4.3 %. The relative frequency is highly among older age groups.⁽³⁸⁾ The highest prevalence has been found in patients with rheumatic and cardiac diseases. No significant correlation has been obtained between the findings of coronary angiography and the activity of macro CK type 1.⁽⁵³⁾

Mitochondrial – CK has been reported in conditions of serious heart muscle damage such as myocarditis, and it has also been mentioned as a presumptive indicator of myocardial cellular necrosis in pediatric patients.⁽⁵³⁾

G. Malignant diseases

Generally, Total CK activity per gram wet tissue appears to be markedly reduced in malignant tumour tissue, yet it is raised in benign tumour tissue.⁽⁵⁷⁾ CK-BB is the predominant isoenzyme in both normal and tumour tissue of the GI tract. Alteration of isoenzyme patterns has been noted between normal and tumour tissue.

Macro CK type 1 is rarely increased in cancer patients and has little apparent value as a tumor marker for these diseases.⁽¹⁸⁾ In contrast, individual macro creatinine kinase type 2 detection has previously been investigated as a potential tumour marker.⁽⁴⁹⁾ The

macro CK type 2 can be detected in 89 % of cancer patients and it cannot be found in healthy subjects. The enzyme abnormalities are thought to stem from tumor tissue.⁽⁴⁷⁾ Increased activities are mainly found in patients with small cell lung cancer and GI tumors (55 %). However, it is rarely increased in cancers of the prostate and breast, and it has little apparent value as a tumor marker for these diseases.

Macro CK type 2 is also not a useful marker of severe liver neoplasia.⁽⁴⁸⁾ Type 2 macro CK has been detected, devoid of any statistical difference, in cirrhosis (14 %), hepatocellular carcinoma (16 %) and metastatic liver tumor (31 %). Furthermore, the presence of type - 2 macro CK is unrelated to the stage of either cirrhosis or hepatocellular carcinoma and lacks prognostic value both in cirrhosis and neoplastic diseases. Neither has it been detected in any patients with leukemia or lymphoma.

Conclusion

Macro CK is a major cause of misdiagnosis of myocardial infarction upon determination of total CK and CK-MB levels. It usually presents in elderly female patients. Based on their compositions, there are two major types of macro CK. Type 1 macro CK is the immune complex of creatine kinase with many types of immunoglobulins. Type 1 creatine kinase has been noted for its correlation with autoimmune diseases, especially the myositis group. Type 2 macro CK is a mitochondrion-derived macro CK present in malignancy, especially small cell lung cancer, gastrointestinal cancer and colorectal cancer. The presence of macro CK type 2 is a poor prognostic sign in patients with malignancy.

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กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งแพทยสภา (ศนพ.) จากการอ่านบทความเรื่อง "Macro creatine kinase" โดยตอบคำถามข้างล่างนี้ ที่ท่านคิดว่าถูกต้องโดยใช้แบบฟอร์มคำตอบท้ายคำถาม โดยสามารถตรวจจำนวนเครดิตได้จาก <http://www.ccme.or.th>

คำถาม - คำตอบ

1. What is the clinical importance of macro creatine kinase.
 - a. It is a hallmark for diagnosis of acute coronary syndrome
 - b. It is a useful diagnostic test for cardiac arrhythmia
 - c. It is a major cause of misdiagnosis of myocardial infarction
 - d. It is an important COENZYME for plaque degeneration
 - e. It is a cofactor in development of myocardial infarction
2. Macro creatine kinase type 1 has been noted for its correlation with?
 - a. Neuritis
 - b. Myositis
 - c. Otitis
 - d. Retinitis
 - e. Hepatitis
3. Which is the best method to identify CK-MB in order to avoid the macro creatine kinase phenomenon?
 - a. Immunoinhibition
 - b. Immunofluorescent
 - c. CK-electrophoresis
 - d. Immunoprecipitation
 - e. HPLC

คำตอบ สำหรับบทความเรื่อง "Macro creatine kinase"

จุฬาลงกรณ์เวชสาร ปีที่ 47 ฉบับที่ 9 เดือนกันยายน พ.ศ. 2546

รหัสสื่อการศึกษาต่อเนื่อง 3-15-201-9010/0309-(1041)

ชื่อ - นามสกุลผู้ขอ CME credit เลขที่ใบประกอบวิชาชีพเวชกรรม.....

ที่อยู่.....

1. (a) (b) (c) (d) (e)

4. (a) (b) (c) (d) (e)

2. (a) (b) (c) (d) (e)

5. (a) (b) (c) (d) (e)

3. (a) (b) (c) (d) (e)

4. Macro creatine kinase type 2 has been reported for its correlation to these cancers except.
 - a. Liver cancer
 - b. GI cancer
 - c. Small cell carcinoma
 - d. Neuroblastoma
 - e. Colorectal cancer

5. Diagnosis of macro creatine kinase can be made if the CK-MB activity exceeds total CK activity by more than what percentage?
 - a. 5
 - b. 10
 - c. 15
 - d. 20
 - e. 25



สถาบันวิทยบริการ

จุฬาลงกรณ์มหาวิทยาลัย

ท่านที่ประสงค์จะได้รับเครดิตการศึกษาต่อเนื่อง (CME credit)
กรุณาส่งคำตอบพร้อมรายละเอียดของท่านตามแบบฟอร์มด้านหน้า

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