Reumatizam 2025;72(1–2):36–39
https://doi.org/10.33004/reumatizam-72-1-2-4

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A REMINDER OF THE CONTINUED RELEVANCE OF MACROENZYME DETECTION TESTING

PODSJETNIK NA KONTINUIRANU RELEVANTNOST TESTIRANJA NA PRISUTNOST MAKROENZIMA

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Received / Primljeno: September 20, 2025 / 20. rujna 2025.
Accepted / Prihvaćeno: December 2, 2025 / 2. prosinca 2025.

Dear Editor,

Although they were much more of a 'hot' topic back in the 1980s, and they are somewhat forgotten nowadays, macroenzymes should still be on the 'radar' of physicians who are working with patients. By their definition, macroenzymes are enzymes, such as transaminase (ALT, AST), amylase, lipase, and even creatinine kinase (CK). These enzymes are bound by immunoglobulins for the most part or polysaccharides in some cases, thus causing falsely elevated laboratory test results since these complexes are not effectively excreted by the kidneys. (1–3) They are generally considered benign, and they often remain undiscovered since they are commonly overlooked, but their relevance prevails. (1–4) The main issue is with physicians who are ordering additional, unnecessary, and sometimes invasive tests for further workup, or modifying effective treatment. This problem, when it is not recognized, actively burdens the healthcare system as well as the patients. (1–3) We have witnessed a handful of such cases firsthand, and one recent case comes to mind when we are discussing this topic. That is the case of a young man who underwent a number of tests before his diagnosis of macro-creatine kinase was confirmed, and this specific case serves as an excellent example of the aforementioned issue.

Poštovani uredniče,

makroenzimi, koji su 1980-ih bili goruća tema, za razliku od danas kada su malo pali u zaborav, bi i dalje trebali biti u fokusu liječnika koji rade s pacijentima. Prema svojoj definiciji, makroenzimi su enzimi poput transaminaze (ALT, AST), amilaze, lipaze, pa čak i kreatinin kinaze (CK). Ovi enzimi uglavnom se vežu za imunoglobuline ili, u nekim slučajevima, za polisaharide, što uzrokuje lažno povišene rezultate laboratorijskih testova jer se ti kompleksi ne izlučuju učinkovito putem bubrega. (1–3) Općenito se smatraju benignima i često zbog previda ostaju neotkriveni, ali svejedno su relevantni. (1–4) Glavni problem predstavlja praksa liječnika koji naručuju dodatne, nepotrebne, a ponekad i invazivne pretrage za daljnju obradu ili modificiraju terapiju koja se već pokazala učinkovitom. Ovaj problem, u slučajevima u kojima ostane neprepoznat, aktivno opterećuje zdravstveni sustav, kao i same pacijente. (1–3) Imali smo priliku izravno svjedočiti nekolicini takvih slučajeva, a jedan od njih, koji se nedavno dogodio, htjeli bismo detaljnije opisati. Radi se o slučaju mladića koji je morao obaviti razne pretrage prije nego što mu je potvrđena dijagnoza makro-kreatin kinaze (makro CK), a taj konkretni slučaj služi nam kao izvrstan primjer prethodno spomenutog problema.

The case subject is a young male patient, 27 years old at the time, who was referred to a rheumatologist due to elevated CK levels. During a routine check-up, slightly elevated AST and ALT levels (115 U/L and 91 U/L) were found, and this finding was later supplemented with a finding of significantly elevated CK levels (8267 U/L). As the patient is physically active and exercises regularly, his CK levels were re-tested after a period of rest, and they were significantly elevated (3626 U/L). The patient did not report any signs of muscle weakness, skin rash, or other symptoms. Liver enzymes were found to be elevated before, approximately two years ago, and at that time serological testing for hepatotropic viruses and abdominal ultrasound were done. The results showed no evidence of abnormalities. At the time of referral, about a year had passed from a partial thyroidectomy, and the patient has been regularly taking a levothyroxine replacement drug. During further follow-up and workup, the patient remained asymptomatic, his CK levels were stable, and the ordered test results showed no abnormalities: myositis autoantibodies were tested and the result was negative, alpha-glucosidase activity result (to exclude Pompe disease) was unremarkable, and electromyoneurography (EMNG) findings did not show any signs of myopathy. The patient was examined by a neurologist, and cervical spine magnetic resonance imaging (MRI) was ordered. The results came back as normal. In the end, the presence of macroenzymes was considered, and testing was performed. The results were indicative of macroenzyme presence, thus confirming a final diagnosis of macro-creatinine kinase which served as an explanation for elevated CK levels. Perhaps elevated AST and ALT levels could be explained by macroenzymes as well, but tests were not performed to confirm this theory.

Macroenzymes can be found in healthy individuals, and they have been described in other cases (even iatrogenic, infective, and post-traumatic), but they are also associated with an autoimmune and lymphoproliferative disease, with the implication of polyclonal gammopathy, which is just one of the explanations for this phenomenon. (1–3) Interestingly enough, polyclonal gammopathy which was found in some cases of liver disease has also been shown to cause macroenzyme development. (2)

There are several methods which can be used to indirectly determine the presence of macroenzymes. One of them is polyethylene glycol (PEG) precipitation, a relatively simple and accessible test, already used in many laboratories for macroprolactin testing, which is a common laboratory procedure. (5) In short, the CK level is measured, and then PEG is applied which causes macroenzymes to precipitate, and following that the CK level is measured again. If there

U ovom slučaju ispitanik je bio mladi muškarac, koji je u trenutku ispitivanja imao 27 godina, koji je upućen reumatologu zbog povišenih razina CK. Tijekom rutinskog pregleda utvrđene su blago povišene razine AST i ALT (115 U/L i 91 U/L), a kasnije su utvrđene i značajno povišene razine CK (8267 U/L). Budući da je pacijent fizički aktivan i redovito vježba, testiranje razine CK ponovljeno je nakon ciklusa odmora i tada su utvrđene značajno povišene razine CK (3626 U/L). Pacijent nije primijetio slabost mišića, osip na koži ili druge simptome. Jetreni enzimi bili su povišeni i prije otprilike dvije godine, a u to vrijeme obavljeno je serološko testiranje na virusne hepatitise i ultrazvuk abdomena. Rezultati su bili u granicama normale. U vrijeme pacijentovog upućivanja na pregled prošlo je oko godinu dana od parcijalne tireoidektomije, a pacijent redovito uzima nadomjesnu terapiju levotiroksinom. Tijekom daljnjeg praćenja i obrade, pacijent nije pokazivao nikakve simptome, razine CK bile su u normalnim granicama, kao i rezultati naručenih pretraga: testirana su autoantitijela za miozitis i nalaz je bio negativan, nalaz aktivnosti alfa-glukozidaze (za isključivanje Pompeove bolesti) bio je bez osobitosti, a nalaz elektromioneurografije (EMNG) nije pokazao nikakve znakove miopatije. Pacijenta je pregledao neurolog te ga je uputio na magnetsku rezonancu (MR) kralježnice. Rezultati su bili u granicama normale. Na kraju je u obzir uzeta prisutnost makroenzima te je provedeno testiranje. Rezultati su ukazali na prisutnost makroenzima, čime je potvrđena konačna dijagnoza makrokreatinin kinaze kojom su se objasnile povišene razine CK. Možda bi se i povišene razine AST i ALT mogle objasniti makroenzimima, ali nije provedeno testiranje kojim bi se ta teorija potvrdila.

Makroenzimi mogu biti prisutni i kod zdravih osoba, a opisani su i u drugim bolestima (čak i jatrogenim, infektivnim i posttraumatskim). Također su povezani s autoimunom i limfoproliferativnom bolešću, uz implikaciju poliklonske gamapatije, što je samo jedno od objašnjenja za ovaj fenomen. (1–3) Zanimljiva je činjenica da se uspjelo utvrditi da poliklonska gamapatija, koja je pronađena u nekim slučajevima bolesti jetre, također uzrokuje razvoj makroenzima. (2)

Postoji nekoliko metoda koje se mogu upotrebljavati za neizravno određivanje prisutnosti makroenzima. Jedna od njih je precipitacija polietilen glikolom (PEG), relativno jednostavan i pristupačan test koji se već upotrebljava u mnogim laboratorijima za testiranje makroprolaktina, što je uobičajeni laboratorijski postupak. (5) Ukratko rečeno, u sklopu tog postupka mjeri se razina CK, zatim se nanosi PEG koji uzrokuje precipitaciju makroenzima, a nakon toga se ponovno mjeri razina CK. Ako se utvrdi značajan pad razine CK između mjerenja, to se smatra potvrdom prisutnosti makroenzima. (5)

is a significant decrease between the measurements, this is considered as confirmation of macroenzyme presence. (5)

It is important to reiterate the importance of macroenzymes, but it is also important to note that, besides causing falsely elevated test results and confusion, some macroenzyme-related results may lead doctors to order more unnecessary tests, thus causing additional strain on the healthcare system, cost and patients. (1–4) One extreme example comes to mind in which the case subject was a patient with elevated AST levels, who ultimately underwent a liver biopsy procedure, a test which is quite invasive and carries certain risks. Following a liver biopsy, the diagnostic tests for macro-AST were performed and a macro-AST diagnosis was confirmed. (4) Another potential issue is the modification of effective treatment, during which the patient's condition remained stable, due to mistaking macroenzymes for iatrogenic toxicity, which can possibly lead to the selection of alternative and less effective treatment options and disease exacerbation. (1–3)

Although it would not be prudent to only test for macroenzymes, in most applicable cases their consideration is certainly warranted, especially in seemingly healthy individuals, and potentially in other unclear cases. Although the popularity of macroenzymes as a topic has waned over the years, they continue to be relevant, and any practicing physician should be informed about this laboratory anomaly when interpreting test results.

Author Contributions: Article conception and design: DVS, MS, SN. Data acquisition, analysis and interpretation: DVS, MS, SSN. Article drafting: DVS, MS, SN. Critical revision of important intellectual content: DVS, MS, SN.

Acknowledgments: The authors report no acknowledgments.

Funding: For this work authors did not receive any funding.

Conflict of interest statement: The authors declare that they have no conflict of interest relevant to this manuscript.

Važno je ponovno naglasiti važnost makroenzima, ali je također bitno napomenuti da, osim što uzrokuju lažno povišene rezultate testova i opću zbunjenost, neki rezultati povezani s prisutnošću makroenzima mogu navesti liječnike na naručivanje dodatnih nepotrebnih pretraga, što uzrokuje dodatno opterećenje zdravstvenog sustava, troškova i pacijenata. (1–4) U skladu s time, dobro bi bilo opisati jedan ekstreman primjer takve situacije u kojem je ispitanik bio pacijent s povišenim razinama AST, koji je na kraju podvrgnut postupku biopsije jetre, poprilično invazivnoj pretrazi koja nosi određene rizike. Nakon biopsije jetre provedeni su dijagnostički testovi za makro AST i potvrđena je dijagnoza makro AST-a. (4) Drugi potencijalni problem predstavlja modifikacija učinkovite terapije (kojom se uspješno održavalo stabilno stanje pacijenta) zbog krive dijagnoze jatrogenih komplikacija umjesto prisutnosti makroenzima, što može dovesti do odabira alternativnih i manje učinkovitih terapijskih metoda i pogoršanja bolesti. (1–3)

Iako ne bi bilo razborito testirati samo makroenzime, u većini primjenjivih slučajeva svakako je opravdano razmotriti njihovu prisutnost, posebice kod naizgled zdravih osoba, a potencijalno i u drugim nejasnim slučajevima. Iako je tema makroenzima doživjela pad popularnosti tijekom zadnjih nekoliko godina, oni su i dalje relevantni i svaki liječnik bi trebao biti informiran o ovoj laboratorijskoj anomaliji prilikom tumačenja rezultata pretraga.

Doprinosi autora: Koncepcija i dizajn rada: DVS, MS, SN. Prikupljanje, analiza i interpretacija podataka: DVS, MS, SSN. Izrada rada: DVS, MS, SN. Kritička revizija važnog intelektualnog sadržaja: DVS, MS, SN.

Zahvala: Autori nisu naveli zahvale za ovaj rad.

Financiranje: Autori za ovaj rad nisu primili nikakva sredstva.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

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