CKing Precision in the Interpretation of Diagnostic Biomarkers

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Creatine kinase (CK) is a dimeric globular protein that includes 2 subunits. The different combinations of the 2 subunits of the CK dimer, CK-M and CK-B, lead to 3 isoforms of the cytoplasmic enzyme. CK-MM is primarily expressed in skeletal muscles and represents the greater part of serum CK. Two isoenzymes also exist in mitochondria. From a physiological perspective, CK is vital to catalyze the reversible exchange of high-energy phosphate bonds, which is crucial for energy buffering in tissues with variable energy demand, such as skeletal muscles. From a clinical perspective, the measurement of CK, a biomarker of muscle damage, is a routine part of the assessment of patients with several conditions.

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intolerance, preventing more severe muscle damage, and all the while trying to maximize the cardiovascular benefits of statins.

Given that a quarter of individuals >40 years are prescribed a statin in the United States, that 7% to 29% of statin users report muscle complaints, and the deleterious effects of statin nonadherence on clinical outcomes, an incorrect diagnosis can have significance consequences, not only for a given individual but also ultimately at a population level. Fortuitous asymptomatic CK levels above the URL can also lead to unplanned and unnecessary follow-up visits. Thus, precisely defining the URL for CK (and other biomarkers) for each individual is a necessity in the clinic.

Yet, for CK and many biomarkers, diagnostic thresholds are uniformly used in all patients, or adjusted on the basis of sex, and may be solely and inappropriately based on the manufacturer recommendations. For example, the URL of CK has generally been proposed to be of =200 IU/L. This is despite the well-established notion that a high proportion of individuals present higher physiological values than previously proposed URLs. Thus, relying on suboptimal URLs may lead to individuals who would benefit from a statin not being treated with one, or to treatment being inappropriately interrupted for safety concerns in already treated patients. Given that sex, ethnicity, and recent physical activity have an important impact on CK levels, they should be taken into consideration when interpreting CK levels in the clinic.

In this issue, Siddiqui et al have further investigated the contribution of CKM Glu83Gly (rs11559024) in explaining the variability in CK levels and whether or not it could help identify patients at a higher risk of statin-induced myalgia. CKM encodes for 1 of the 2 CK dimers, CK-M. The study by Siddiqui et al builds on previous reports from our and other groups which have found that genetic variants in the CKM gene influence CK levels. In the current study, the authors have further validated the association between the rs11559024 variant (Glu83Gly) in the CKM gene and baseline CK levels in the GoDARTS (Genetics of Diabetes Audit and Research, Tayside Scotland) and JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) populations. This association was observed in each study individually and in a meta-analysis of the 2 studies and confirms that carriers of the rarer variant present significantly lower CKs than noncarriers. In these 2 cohorts, the minor allele frequencies (0.02 and 0.018) were similar to those we observed in whites (0.01). In an Icelandic cohort of 63,159 individuals, the reported allele frequency was 0.0215. Consistent with previous reports, Siddiqui et al found that the association between CKM Glu83Gly and CK levels is independent of statin use.
The novelty of the findings presented by Siddiqui et al. lies in the longitudinal nature of the GoDARTS study, which has allowed the investigation of intra-individual variability of CK levels by genotype. They found that Gly83 carriers presented a significantly more limited intra-individual variability. This suggests that Gly83 carriers have a lower CK inducibility than non-carriers, which, as highlighted by the authors, goes to the essence of the measurement of CK as a biomarker, namely increasing levels in the presence of muscle damage.

This limited inducibility is further illustrated by the case of the sole Gly83Gly homozygote from GoDARTS. The authors have provided additional information on this fascinating case. Specifically, the authors describe that despite experiencing episodes of necrotizing fasciitis, and subsequent gangrene with a debridement procedure, the CK levels never exceeded 28 IU/L and rose to only 34 IU/L after a hemicolectomy for bowel cancer. The patient had also been reported to present statin intolerance with CK levels always deemed normal by clinicians looking for evidence of statin-induced myopathy.

Furthermore, in the current article, Siddiqui et al. found that the CKM Glu83Gly variant did not influence the risk of rosuvastatin-induced myalgia in JUPITER, a carefully conducted randomized, placebo-controlled trial. This is consistent with a previous observation that this genetic variant is not associated with statin intolerance. Nevertheless, it is important to highlight that in JUPITER, as in most randomized controlled double-blind trials and observational studies, no dedicated questionnaire to query patients systematically about muscle complaints was used. Alas, it has become apparent during recent years that the difficulty in identifying genetic risk factors of statin-induced myalgia may lie in the lack of precision in defining it compared with more severe manifestations, such as rhabdomyolysis. The need to validate proposed SAMS assessment tools has been highlighted and is paramount to the discovery of SAMS genetic factors.

Thus, in summary, the study by Siddiqui et al. indicates that although the Glu83Gly variant may not be useful in identifying individuals most likely to develop statin-induced muscle complaints, it could perhaps help clinicians to interpret low CK levels in the presence of muscle damage in patients with suspected SAMS or any other diagnosis using CK. As highlighted by the authors, although an allele frequency of 0.02 translates into low carrier prevalence, on a global level, given the growing number on statin users, this could represent a significant number of individuals. This hypothesis requires prospective validation.

What are the next steps that need to be taken to further personalize diagnostic thresholds of CK in patients with SAMS? Certainly, using URLs that take into consideration established clinical determinants, such as sex and ethnicity, appears a necessary first step, and this approach is now advocated by some professional societies. From a genetic perspective, as more than a dozen rare and common variants have been associated with CK levels, including low frequency nonsynonymous variants in the CKM gene, one can contemplate the creation of genetic risk scores to summarize their global impact, such as those developed to predict coronary heart disease, as well as the benefit of statins.

such an approach could help identify individuals who have a genetic predisposition to high physiological CK levels and enable adjusting the URL to reduce the number of erroneous false-positive results that can lead to unnecessary additional investigation or statin withdrawal. Alternatively, it could identify individuals who could present SAMS without increased CK levels and for whom CK represents a less reliable biomarker because of a lesser CK inducibility and in whom muscle damage may be erroneously excluded.

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