Cardiac Troponin to Adjudicate Subclinical Heart Failure in Diabetic Patients and a Murine Model of Metabolic Syndrome

Article:
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Cardiac Troponin to Adjudicate Subclinical Heart Failure in Diabetic Patients and a Murine Model of Metabolic Syndrome.
J Appl Lab Med 2024; 9(6): 913–26. https://doi.org/10.1093/jalm/jfae091

Guest: Dr. Chris Farnsworth from the Department of Pathology & Immunology at Washington University in St. Louis.

Randye Kaye: Hello and welcome to this edition of *JALM* Talk, from *The Journal of Applied Laboratory Medicine*, a publication of the Association for Diagnostics & Laboratory Medicine. I'm your host, Randye Kaye.

In 2023, the American Heart Association released a Presidential Advisory that recognized and defined "CKM syndrome," with CKM standing for Cardiovascular-Kidney-Metabolic, as a health disorder attributable to connections among obesity, diabetes, chronic kidney disease, and cardiovascular disease. CKM syndrome significantly raises the risk of heart failure and other cardiovascular complications. The American Heart Association guideline proposed a staging system for CKM syndrome that incorporates cardiac biomarkers to detect subclinical cardiovascular disease. High-sensitivity cardiac troponins are among those biomarkers. While high-sensitivity cardiac troponins are well established biomarkers of myocardial injury and acute coronary syndrome, there is a lack of consensus regarding the appropriate cutoffs to use for heart failure staging in patients with diabetes or with CKM syndrome.

The November 2024 issue of *JALM* features an article that explores the associations among cardiac troponin I and multiple clinical factors implicated in CKM syndrome. The authors assessed cardiac troponin I in outpatients and associated the results with cardiac comorbidities, demographics and estimated glomerular filtration rate. Today we're joined by the article's corresponding author, Dr. Chris Farnsworth. Dr. Farnsworth is an associate professor of pathology and immunology at Washington University in St. Louis and the medical director of clinical chemistry and point of care testing at Barnes Jewish Hospital. His research interests include prognostication of diseases using cardiac biomarkers, laboratory testing at the host pathogen interface and pre-analytical errors in laboratory testing. Welcome Dr. Farnsworth.

Chris Farnsworth: Thank you for having me for this discussion.

Randye Kaye: Let's start with this. We typically hear about the use of cardiac troponins as biomarkers for acute myocardial infarction most often in an emergency room setting. What prompted you to assess cardiac troponin in a population of outpatients with diabetes?

Chris Farnsworth: I think that one could say arguably that cardiac troponin is the most successful biomarker we've ever seen in laboratory medicine and I think that one of the reasons for that is its absolute specificity for cardiac damage. So, well historically this has meant that it applies specifically to myocardial infarction. I think more recently we've seen troponin use for a host of other potential non-ischemic mechanisms of cardiac damage. For example, the field of cardio-oncology is this entire field of cardiology that's focused on potential damage to the heart from chemotherapy such as Herceptin, and we're seeing biomarkers start to emerge in that field, specifically troponin and some others for potential use for actually detecting and assessing cardiac damage.

What we've learned with troponin is that it can be used to also prognosticate future cardiac events and back in the UK, there are some assays that have been cleared for use and included in the pack of insured claims for prognostication of future cardiac events. So actually even in the US now, we started to see some assays. For example, the Siemens assay just recently gained clearance from the FDA to extend their IFU to include future cardiac event risk based on these new FDA cleared prognostication risk claims.

So now we're not just thinking of troponin as something that we can use for acute myocardial ischemia or heart attack, but also a means of risk stratification almost in the same way we do lipids now. So a good deal of work has generally been done in healthy populations demonstrating increased risk in patients with elevated troponin. But there's been a lot less in diabetic populations, and the diabetic population is actually quite complex clinically as they have this constellation of diseases that we referred to in the intro, known as CKM syndrome. So CKM stands for Cardiovascular-Kidney-Metabolic syndrome. These patients often have obesity and associated systemic inflammation. They have diabetes, which also associates with chronic kidney disease and cardiovascular disease. So all these things can impact circulating biomarkers to various degrees. And if we were to zoom out and ask, "What are we really trying to answer here?" It's, "What is the association of cardiac troponin and outcomes and patients with CKM or some type of diabetic syndrome, and what are the specific thresholds that we can use to risk stratify these patients?"

Randye Kaye: All right. Thank you. So in the article you mentioned that different societies have different recommendations with regards to biomarker screening for subclinical heart failures. So what are these recommendations and why are they different?

Chris Farnsworth: Yeah. So with the advent of high-sensitivity troponin assays, we can now measure circulating troponin accurately in at least 50% of the presumably healthy population. So as many listeners probably know, the 99th percentile upper reference limit is what we're typically using as the definition of myocardial injury regardless of the clinical setting, whether the emergency department or outpatient or wherever we might see a patient. What we've learned from other studies is that troponin even below the 99th percentile upper reference limit, but it's still measurable, can actually be used to prognosticate future major adverse cardiac events, or MACE.

As I mentioned, there's an assay in Europe that's cleared for this purpose with thresholds of 10 nanograms per liter for females and 12 nanograms per liter for males, despite the 99th percentile for that same assay being closer to 17 and 35 for females and males, respectively. So the problem with CKM syndrome and the use of cardiac markers for this purpose, is that we don't really have good thresholds for determining where there's actually increased risk for future events. As a result, the American Heart Association actually uses the risk thresholds of 10 and 12, which I just described that are used in Europe for troponin I as the diagnostic criteria for subclinical heart failure, despite the real complete lack of data in the CKM population for that threshold.

So similarly, the ADA actually makes their own recommendations, and they recommend the use of the 99th percentile upper reference limit, which again is the definition of myocardial injury for troponin, as the threshold for increased risk of future events in providing more aggressive treatment. So as a male, for example, one guideline recommends that you use 12 nanograms per liter, and another recommends that you use 35 nanograms per liter on one specific assay. So there's definitely differences. And the other thing I want to point out here is that societies recommend that troponin and natriuretic peptides are actually measured annually in these patients, so they have different thresholds, but they want you to measure them at least once a year. I think there are a few problems with this approach towards biomarkers specifically for CKM, but the main issue in my mind is not that one is almost three times higher of a cutoff than the other, but rather we don't really have evidence to support either. So both could be wrong or perhaps there could be a better cutoff specifically in CKM syndrome.

Randye Kaye: All right, that's a lot. So can you summarize the key findings from your study then?

Chris Farnsworth: So we tested 1,500 patients approximately, with suspicion for or previously diagnosed diabetes using cardiac troponin I with the long-term goal of assessing outcomes in patients and defining these ideal thresholds. However, outcomes data takes a long time to get. So in the absence of that, we really wanted to ask what is the impact of just applying current society-endorsed thresholds -- the ones that I just mentioned for high-sensitivity troponin for subclinical heart failure on this outpatient diabetic or presumably diabetic population. What we found was it 8% of females and almost 16% of males had troponin I concentrations above the risk threshold of 10 and 12 nanograms that are endorsed by the AHA and then using the 99th percentile, 4.2% of females and 4.1% of males were above the sex specific, which again is what's endorsed by the ADA. So regardless of the thresholds you use, there's a significant portion of people with troponin above the threshold for increased risk in subclinical heart failure. As I mentioned above, guidelines recommend that this is assessed annually, but we also found that most of these patients had no diagnosis associated with subclinical heart failure, potentially implying that most of this risk was going undetected by physicians.

Randye Kaye: Thank you. So here's another question, your study, it also incorporated animal studies that modeled human obesity and type 2 diabetes in mice, and you demonstrated that those mice also had elevated troponin. So how well does the mouse model represent the human disease, and what should we make of this observation?

Chris Farnsworth: Yeah. So before we enter the animal model, I'll mention that one of our other interests was really to try to figure out or parse apart what portion or what component of CKM syndrome most associates with this increased troponin. As I mentioned, it's kind of a constellation of disease, of kidney disease and cardiac damage and diabetes and increased glucose. So what we actually did first is we performed chart review on those 1,500 patients and we found that the presence of renal failure and the diagnosis of heart failure most associated with elevated troponin.

However, we also saw that increased glucose alone was also potentially predictive in some of our models, which is in itself interesting because our knowledge of glucose control alone has never really been shown to associate with increased troponin. So that's where the mouse model came in. So we use this mouse model called C57 Black 6 and it's a model of obesity and diabetes where you basically give these mice a diet of 60% kilocalories from fat for three months and they

actually become overweight and have features that really mimic type 2 diabetes, just like we see in in humans.

So they have elevated glucose, they have insulin resistance, they have a large amount of adiposity, and they're generally overweight. I think importantly what makes it a little bit different of a model than what we see in humans is that this mouse model doesn't really develop renal dysfunction and they don't really have early stage heart failure. So it actually really is kind of a control for just what is the impact of obesity and diabetes. So all we did is we just tested troponin on these two animals, the control and the high-fat mouse. We found that there was twofold higher troponin in those that had the high fat diet compared to those that were control mice. So this implies perhaps that glucose and the associated inflammation from a high-fat diet may be sufficient to cause some degree of cardiac damage.

Randye Kaye: Oh, my last question here. What do you think are the key clinical findings that readers should take away?

Chris Farnsworth: Yeah, I think it kind of boils down to this. So I think this study provides evidence that really there's a high proportion of diabetic outpatients that are meeting the criteria for subclinical heart failure using high-sensitivity cardiac troponin measurements. I think it will also show that glucose control is potentially independently associated with elevated troponin, which we found in both the humans, but as well as in the murine mouse model. And I think this really emphasizes the importance of glucose control as a predictor of cardiac damage. I think more importantly, what we really need are outcomes-based studies that establish ideal thresholds for this diagnosis of subclinical heart failure, contrary to the approaches that we're currently taking with our guidelines that really associate with increased adverse coronary events and the risk of those, as well as some treatment thresholds in patients with CKM syndrome.

Randye Kaye: All right. Thank you so much and thanks for joining us today.

Chris Farnsworth: My pleasure. Thank you.

Randye Kaye: That was Dr. Chris Farnsworth from Washington University in St. Louis describing the *JALM* article "Cardiac troponin to adjudicate subclinical heart failure in diabetic patients and a murine model of metabolic syndrome." Thanks for tuning into this episode of *JALM* Talk. See you next time and don't forget to submit something for us to talk about.