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Definition and staging of CKM syndrome

Dr. Lam:
Let me try to very quickly summarize for you what the CKM syndrome is.

Here are my disclosures.

Here is a very simple definition: The cardiovascular-kidney-metabolic, or CKM, syndrome is basically a health disorder due to the connections among the C, heart; K, kidney; M, diabetes; and obesity. And this leads to poor health outcomes, particularly cardiovascular disease events. A few things I want you to notice straight away. First thing, when we say cardiovascular disease, we actually refer much more than just to acute myocardial infarction and coronary heart disease; we're also talking about heart failure, atrial fibrillation, along with, of course, coronary heart disease, but also stroke and peripheral artery disease. So the whole spectrum of cardiovascular disease.

The other thing to notice is that the CKM syndrome construct is actually really focused on cardiovascular risk, and the poor outcomes are really focused on cardiovascular events. Now, is this fair? Well, as cardiologists, we think so, because we do know that among patients with kidney disease, among patients with obesity, the cause of death, eventually, and hospitalization tends to be cardiovascular events. So that's one of the strengths, but also has been some of the sort of questions about whether it should just be focused primarily on cardiovascular events.

Another thing to notice, the syndrome definition includes both individuals at risk for the syndrome and those with existing cardiovascular disease. At risk and existing cardiovascular disease.

And then the third thing, notice, I never said CKM disease. It's CKM syndrome, and we have to be reminded what a syndrome is. When we say a syndrome, that means a collection of clinical features that we need to recognize. And this is a deliberate thing that we want to try to recognize, this syndrome, a collection of features that are linked by a common pathophysiology. And what is that common pathophysiology? It is basically as depicted here, inflammation, oxidative stress, insulin resistance, vascular dysfunction, macro- and microvascular disease. And these are really, really the central underpinnings that are postulated to then impact the heart, the kidneys, the interactions between them, and be linked in the first place by an inflammatory milieu of obesity and insulin resistance. So this is the CKM syndrome.

Finally, please note, it’s actually a systemic disorder. It's not just one organ. It's, of course, multiple organs. Now this overlap of these organ systems, how often does this overlap occur? I mean, why do we even have to name this new collection of clinical features? Well, this data really show us that it is commonly associated. These are data from the US population, and here you can see that prevalence of one of these conditions, of either type 2 diabetes, kidney disease, or cardiovascular disease, is actually in more than 25% of patients, of whom 1.5%, but of the US population that's almost 4 million, have all 3, and that's right in the center of that overlapping graph. And then you see the dyads, or the 2 of them occurring together. The most common is actually type 2 diabetes and chronic kidney disease, and that's 3.2, or 8 million people. And then the second most common would be type 2 diabetes and cardiovascular disease, which impacts almost 4 million people. And then finally, cardiovascular disease and kidney disease, another 4 million people. So this is a lot of people. This is just the US population.

Also, by the way, linking this together like this really emphasizes to us that we have been very siloed. We move from thinking of the heart alone, and then we started thinking about the interactions of the heart and the kidney. We call that the cardiorenal syndrome. I'm sure you know that. And then I'm sure you've also heard of cardiometabolic syndrome, and so that's when we're thinking of type 2 diabetes and the heart. But even those 2 dyads are actually silos, and so this coming together to call it the CKM syndrome is really to try to recognize that this is one in the same patient in many cases, and that we need to start thinking of that patient holistically.

Now I'd like to show you the novel CKM staging model. Why are we staging? It's of course to recognize that the CKM syndrome is progressive, and the whole point there is to try to manage the condition throughout the stages for prevention and to push patients back towards health. So you start with stage 0, and that's where there's no risk factors, no obesity, no hyperglycemia, no hypertension, no hyperlipidemia. And here, if anyone is at stage 0, the whole focus of management is primordial prevention and keep the patient from developing any of the risk factors and from progressing to, of course, stage 1, which is really focused on either too much or unhealthy adipose tissue. So I say that carefully: It's either quantity or quality of adipose tissue that's not good.

Now, how do we measure that? Well, we can use body weight, but there's also an emphasis on where that body weight and fat distribution is, so central adiposity is emerged. And what I really like about the definition of stage 1, if you look up the document, it actually specifically calls out that in some populations, like Asian ethnicities, we should be using specific cutoffs. For BMI, for example, the Asian cutoff is only 25 for obesity, and for waist circumference it's actually 80 cm only for women and 90 cm for men. And that's recognizing that certain ethnicities are predisposed to metabolic abnormalities at lower cutoffs. So that's very good. The second thing that it specifically calls out is women with gestational diabetes, who would again fall under here as people who need to be monitored for development of diabetes in future.

Now, stage 2. What happens in stage 2? You actually have metabolic risk factors, and they're familiar to us: hypertension, hypertriglyceridemia, or frank type 2 diabetes. Of course, if you fulfill metabolic syndrome, you're in stage 2. And then notes that there is mention of moderate- to high-risk chronic kidney disease. What defines moderate or high risk? Well, this is the KDIGO staging, and you'll see that later, but I just want you to remember for now, the KGIDO staging actually separates patients into risk groups based on 2 variables, the GFR and urinary albumin-to-creatinine ratio. Right? Now, what that means, of course, is in order to evaluate patients, we need to know both GFR and uACR. Now, for the nephrologists sitting out there, you're probably going, “Yeah, and?” but for the cardiologists sitting out there, give me a show of hands who actually measures uACR in your patients? Cardiologists? Oh, okay. Bravo. Truly, truly, that's really excellent. But that is the message, right, that we need to measure.

Now, note these little curvy arrows that come in from the outside. So we're not excluding patients who develop hypertension or diabetes in the absence of adiposity. And so you see, the non-metabolic etiologies of hypertension or CKD come in that way, and that's because the management and the staging from henceforth is the same. Okay?

And then you reach stage 3. Now this one is really, really important. What is this stage? It's subclinical cardiovascular disease. And what do we mean by that? It means the patient is not going to announce to you, “I have subclinical cardiovascular disease.” Obviously, it's subclinical, so they don't have the symptoms, and it's our responsibility to detect it. And why? Because this is a high-risk stage where preventive intervention is really, really important. Here's where we get big bang for the buck. Okay? We make the effort to detect subclinical disease. We now have treatments that you hear about that can actually prevent the onset of clinical disease. So this is very, very important, and don't forget, it also includes staging of the kidney disease.

And finally, you can imagine, in stage 4 is the clinical cardiovascular disease. And in this stage, it's also divided into 2 substages, by the way. 4a is those with end-stage kidney disease, and 4a without the kidney disease, and 4b with severe kidney disease.

How common are these stages? And here I'm very pleased to present Muthu’s work actually, published in JAMA, really showing that in NHANES, when he looked at the data from 2011 to 2020 what's not shown here is the major take-home message that 90% of the US population had some stage of CKM, which is stage 1 and above, 90%. And 15% had advanced CKM, which is 3 or 4. And then if you look at the breakdown, you can see that stage 1 is there in about 25%, stage 2 in almost 50%, and then stage 3 and stage 4 in a smaller but very important sizable percent.

So here, I've really summarized, first, what the CKM syndrome is, what the stages are, and how they're defined. And just a reminder that the whole rationale is to reflect the pathophysiology and the interactions of these 3 organ systems that very commonly occur together and that we should be paying attention to because we have therapies that can actually regress these stages. It's very important that the staging is a reminder to us to detect early stages early for management. And, in totality, calling it this syndrome is really reminding us to treat the patient holistically rather than in silos.