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## 3 Things You Need to Know About Calciphylaxis: Earlier Intervention, Current Treatments, and Emerging Therapies

### Announcer:

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### Dr. Sinha:

Calciphylaxis, also called calcific uremic arteriopathy, is a rare and serious complication most frequently seen in patients with chronic kidney disease and largely in those patients who have end-stage kidney disease, or ESKD for short. And if it's not managed properly, calciphylaxis can be fatal within a year, so there's a really high unmet need for us to find some medical therapies and also some strategies to make life better for these patients. Today we're going to look at how we can reach an early diagnosis of calciphylaxis but also how emerging therapies will hopefully complement our current treatment plans for our patients.

This is CME on ReachMD, and I'm Professor Smeeta Sinha.

### Dr. Nigwekar:

And I'm Dr. Sagar Nigwekar.

### Dr. Sinha:

So to start things off, Sagar, you are quite the expert on calciphylaxis, so what can you tell us about the signs and symptoms that should raise our suspicion of calciphylaxis in our patients? Because not everybody will know as much as you do.

### Dr. Nigwekar:

Thank you, Dr. Sinha, for that question. To begin with, I mean, calciphylaxis can have a very variable presentation. So having a high index of suspicion for this diagnosis is important from the clinical diagnosis perspective. The most common way that calciphylaxis patients will manifest will be with painful skin lesions, and in the early part of the presentation, these lesions may look quite benign, such as plaque or maybe simple nodule on the skin. The location of these lesions can be important and can provide a clue in terms of early diagnosis, especially if they are in the areas of central body parts, such as the lower part of abdomen or upper part of thighs. That can be a suggestion for the possibility of calciphylaxis when the patient is presenting with painful skin lesion. The ulcer, if it has already happened, which unfortunately in many patients it does happen, it typically is dry. It is not a red ulcer, so you will not appreciate a lot of oozing from the wound, but rather the ulcer will appear on the drier side. On exam, one of the important signs to look for, especially for early diagnosis, is a purplish or a pinkish discoloration of the skin around the area of those nodules or the plaques. And that, accompanied by tenderness or painful-to-touch areas, really makes us think about the possibility of calciphylaxis in the early part of its presentation.

### Dr. Sinha:

So thank you, Sagar, for giving us an overview on the signs and symptoms to look out for. But what should we do from a diagnostic point of view if we suspect the disease?

**Dr. Nigwekar:**

Yeah. So that's a very important question, Smeeta. So having a high index of suspicion is going to be important as we think about the possibility of calciphylaxis. In most instances, you know, the diagnosis can be made based on the clinical manifestations and the patient's risk factors. At present, at least in my opinion, there is no confirmatory test. We can use something like a skin biopsy in some cases to rule out the conditions that may look like calciphylaxis, which get referred to as calciphylaxis mimics, but by itself, the biopsy does not have kind of a, quote/unquote, gold standard features to establish the diagnosis of calciphylaxis. There could be potential risks of doing a biopsy, such as a nonhealing ulcer or a potential for infection, so it needs to be carefully thought out.

However, in patients who are presenting with atypical features or patients who have calciphylaxis in the absence of kidney disease, those are some of the situations where a biopsy can be helpful. Another question that comes up in terms of this diagnostic approach: Is there any kind of noninvasive test, like a blood test or an imaging test, that can be done to diagnose calciphylaxis? Unfortunately, at this point we do not have a diagnostic test that meets the sufficient sensitivity or specificity to establish the diagnosis.

**Dr. Sinha:**

Yeah, I couldn't agree with you more: clinical diagnosis but skin biopsy to rule out rather than diagnose. Yeah, great.

**Dr. Nigwekar:**

So then, Smeeta, now that, you know, we have a little bit of understanding of what to look for when we suspect calciphylaxis in our patients with CKD as well as end-stage kidney disease, let's talk about treatment options. So what should be the goals of the treatment? And how can we formulate an effective, multidisciplinary treatment plan to manage these patients with calciphylaxis?

**Dr. Sinha:**

Well, absolutely has to be multidisciplinary, and I think, Sagar, you and I, we're really lucky because we have access to multidisciplinary teams to support us with this. But I think you can probably frame it in terms of, you know, wound management, pain management, advanced care planning, and then therapies that try and address the risk factors of the disease.

So I'll start with wound management. The patients have ulcers largely, and they're open ulcers, so we access our tissue viability nurses in the UK, but I know that in other areas they may use dermatologists, plastic surgeons, or vascular surgeons who can help with the wound itself, also advise when to do things like wound debridement, surgical or on the ward, and also have a greater understanding of the dressings and how to prevent infection in those wounds because our biggest fear is sepsis leading to bacteremia and death. So effective wound management reduces that risk of sepsis as well.

And then we need to look at pain because, Sagar, as you said, pain is often the hallmark of the disease, and it's the thing that really affects people's quality of life to the point where some patients are saying, "Enough. I'd rather stop dialysis than continue." And that's largely because of the pain. So I have access to a palliative care team who have expertise in management of pain, but also there are pain specialists, and some anesthetists are very good at it as well. So I think I would recommend engaging a pain specialist, because as nephrologists, we're just not as good as they are. And a particular advantage with a palliative care team supporting you in pain management is they can also support you with advanced care planning or palliative care, particularly because we sadly know the outcomes are really poor, and we do lose around, depending on which studies you look at, 40 to 60% of patients. So they need to know what lies ahead so that they can make plans for themselves and their loved ones, and it comes back to doing what's right for that patient and that individual, and palliative care teams are really good at supporting pain and advanced care planning.

And then we look at therapies that might try and address the disease or try and prevent progression, and as nephrologists, we will look at the biochemical factors, so the blood results, and try and correct things like calcium phosphate and PTH [parathyroid hormone], and we can do that by adjusting the dialysis by doing more frequent dialysis, or making sure the dialysis adequacy is good. We may also add in pharmacotherapies that can bring down the PTH or help with the calcium and phosphate, so avoiding things like calcium-based binders or using cinacalcet or also withdrawing drugs that might be contributing to calciphylaxis – and, Sagar, again, you mentioned earlier about warfarin being a really common factor associated with the development – so withdrawal of warfarin as well. And then associated with pharmacotherapy and the etiology, we may try and give things like sodium thiosulfate to address that the calcium phosphate – the calcification side of things.

**Dr. Nigwekar:**

So then, Smeeta, can you also provide some perspectives for our listeners in terms of ongoing trials and also potential changes to how we currently manage our patients with calciphylaxis?

**Dr. Sinha:**

There's the CALCIPHYX phase 3 trial, which looks at a novel component called SNF472 – a novel agent, which tries to prevent calcification and seeing how that works in calciphylaxis. And I think we're hoping for the trial results to be available in the next few

months. So that will be our first large rat phase 3 placebo randomized controlled trial in the disease.

There's also a study that's being run out of Australia which is a platform trial, which basically means you can look at lots of different interventions. So they're hoping to look at dialysis, wound care, and potentially some pharmacotherapy.

I don't know what you think, Sagar, because you've been involved in these trials, as well, and what your take on it is and how you think that might change the care that we provide in the future.

For those of you just tuning in, you're listening to CME on Reach It MD. I'm Professor Smeeta Sinha, and here with me today is Dr. Sagar Nigwekar. We're discussing the 3 things you need to know about calciphylaxis. This includes the potential of emerging therapies to complement current treatments for patients with calciphylaxis in CKD or end-stage kidney disease.

**Dr. Nigwekar:**

I think, you know, through the experience with CALCIPHYX trial and also experience that is now coming from some of the registries and hopefully the Australian trial that you mentioned, Smeeta, will also provide evidence in terms of the selection of agents as we approach patients with calciphylaxis – sodium thiosulfate, vitamin K, and then the magnesium are the specific therapies that the Australian trial is investigating.

I also wanted to highlight that very likely we are not going to have 1 treatment that kind of cures calciphylaxis just considering the multiple risk factors that have been identified thus far in terms of development of calciphylaxis. I suspect that this approach of multimodal treatment will likely remain, but obviously a big change in that will be having an inclusion of an approved and systematically studied agent, and that will help not just in terms of improving the wound and the overall, survival of these patients but also the quality of life considering some of these agents also have a specific effect on the pain improvement, and, in fact, the clinical trials that are currently ongoing have all been studying pain improvement as one of their main endpoints.

**Dr. Sinha:**

So I'm going to ask you for one final wrap-up, Sagar. What is your take-home message for our audience?

**Dr. Nigwekar:**

One is, of course, you know, the high suspicion that we have discussed in this podcast so far, and the other one I will include is, you know, to really encourage the patients to participate in the clinical research activities. This disease does not have an experimental or an animal model to really understand it better, so we are relying on patients to devote their time and experience for us to really learn from it and hopefully develop more effective treatments and preventative strategies in future.

**Dr. Sinha:**

So unfortunately, I think I'm going to have to wrap up now because that's all the time we've got today. So I want to thank our audience for listening in and thank you, Sagar, so much for joining me and for sharing all of your valuable insights. It's always a pleasure to talk to you, and I look forward to catching up with you face-to-face.

**Announcer:**

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