Interviews

EMJ spoke with Smeeta Sinha and Nina Gold, who shared their experiences and insights as experts in rare diseases. The topics explored in these interviews include calciphylaxis and the challenges associated with performing rare disease research, and genomic newborn screening and its potential impact on rare genetic disease outcomes.

Featuring Smeeta Sinha and Nina Gold

Smeeta Sinha

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Q1 What initially attracted you to a career in nephrology, and more specifically in rare renal diseases?

I qualified as a doctor in 2000, and in my first year I worked on a renal transplant unit for 6 months, which sparked my interest in nephrology. Obviously, the surgical side was interesting, but what really intrigued me was the fact that the function of these organs can be replaced. There was also so much variety in the specialty, including immunology, and managing people with long term-conditions. It was the wide scope of practice, and the fact that I didn't need to be shoehorned into one particular thing. It was also the enthusiasm of individuals, as everyone I met who did renal seemed to love it. And I can't say I regret it; I love my job, so it was definitely a wise choice.

Q2 You are recognised as an international leader in the field of calciphylaxis. What sparked your interest in this area of nephrology?

I think it came from two avenues. When I was going through my training to be a consultant nephrologist, I wanted to take time to do something different to complement my practice. So, I went back to university to do a laboratory-based PhD in basic science, looking at smooth muscle cells and how they calcified.

While this research had clinical relevance, as individuals with kidney disease often suffer from heart and vascular issues due to vessel calcification, applying my PhD findings in practice wasn't quite as easy as I thought. Then, sadly, I came across a patient who had calciphylaxis, a rare condition that didn't have any treatments or cures. In the organisation I was working at, they had established a registry to try and collect data on people with this rare disease. Since so few people are affected by it, you can't find out what's happening very quickly, which makes it hard to do research, and understand the disease. It was an opportunity to combine something that I had seen somebody suffer with, and try to do something better for them with research. Calciphylaxis is a disorder of vascular calcification, so it allowed me to bring together my PhD and

experience with patients, and gave me the opportunity to do translational research.

I do think we need to be looking at rare diseases as a whole, not just calciphylaxis. Although rare diseases are, by definition, rare, if you add them all up, then over 25% of adults, and over half of all children with kidney failure have a rare disease.[1] To complicate matters, patients don't always get access to the treatments or experts that may help.

Q3 You are currently actively involved in calciphylaxis research. Could you tell us if there are any exciting developments in the field?

Calciphylaxis research has changed a lot over the course of the last 15 years. Back then, it was very much about trying to collect data, and encouraging patients who had calciphylaxis to share their experiences, allow us to collect samples, and follow their progress. That was done via the UK Calciphylaxis Registry, or the UK Calciphylaxis Study that has been running for over a decade; there are similar studies running in Australia and the USA. That allowed us to collect samples, and to do observational research. Simultaneously, there were basic scientists in laboratories who were trying to understand the processes that cause calciphylaxis at a cellular level, and then starting to test potential treatments for it.

In the last 5 years, those therapies have emerged from the lab. They have gone through basic laboratory testing, and are now being evaluated in people. So, we've moved from observational research to doing interventional studies with new therapies. The global, multicentred, randomised controlled trial, the CALCIPHYX study,[2] reported its headline data last November, and I'm sure there will be other studies now that one has been completed.

It's hard to do studies in rare diseases, because there are not enough patients, but I think what the CALCIPHYX study[2] showed was that no disease is too rare; trials can be done, and we shouldn't give up on doing them. My take-home message would be that we've moved from observational studies to interventional studies with new therapies, and the trials are feasible, so we should continue to do them.

It is also good to be able to offer patients something. In the early part of my career, it was very much about pain management, and trying to look after their wounds and dialysis. Patients would ask me, "What's going to happen to me?" I'd have to be honest, and try and explain that, sadly, many people don't get better, and will die from the condition, but we would try to manage their pain and wounds. At least now, whilst I still need to tell them that, I can say, "We have a clinical trial; I don't know what it will show, but there's something I can offer you." Hopefully, in 10 years' time, I'll be having a different conversation, where I could offer them treatments that could cure, or at least significantly improve, their condition.

Q4 In July 2023, you received funding from Kidney Research UK and Kidney Wales to gain a deeper understanding of the lived experiences of patients with calciphylaxis, their family members, and caregivers. Is this research now underway, and have any key themes emerged from the data collected so far?

This is a really important study. I've talked about smooth muscle cells, epidemiology, observational studies, and investigational trials of new therapies, but there are patients who are experiencing the disease throughout this. The research community is rightly placing a much greater emphasis on the importance of patients' experiences and outcomes, as reported by them. We shouldn't be congratulating ourselves if the numbers on a lab report get better, but the patient doesn't feel any better. Patient groups and voices are now actively involved in designing research.

The research grant was funded by Kidney Research UK, to whom we are very grateful, but the idea was very much driven by our patients, their caregivers, and a fantastic researcher called Sharon Hewish in Exeter, UK, who is a postdoctoral dietitian. Again, this shows that it's not just medical doctors and university-based scientists who can do research. All healthcare professionals can shape research, and deliver it.

Hewish is now interviewing patients and their carers. Hopefully we'll have some data by 2025, which will then shape the information we give to patients, and this can inform future trials so that they're patient-focused. The other thing about rare disease patient advocates is that they are often the experts in their disease, so they have a huge amount of information to impart to us as researchers, as well as clinicians. It would be a real missed opportunity not to listen to our experts.

Q5 As a rare disease expert, what have been the main challenges associated with conducting calciphylaxis research, and do you see any additional barriers impairing future research?

In addition to the small numbers of patients with calciphylaxis, people make assumptions about which treatments do and don't work, and some of those treatments don't have an evidence base to support them. However, I do understand why people use them, they want to do something good, and want to try anything based on biological plausibility. However, we now live in a scenario where we can do clinical trials, so I think one of the barriers is clinicians, or researchers not wanting to put their patient forward for a trial. We need to have a research-positive approach, which a lot of my colleagues and I have, but I don't think that's necessarily universal. We can learn from oncology, where clinical trials are embedded into routine practice. Patients will go through their standard treatment, and if they're not responding, or if they're slightly different, they will go into a trial as part of their treatment. I would like to see this in rare diseases, and in kidney research in general.

In the calciphylaxis field, I would like to see clinicians saying, "This is your disease, this is what we're going to do, and a clinical trial is one of the things we can offer you." If we embed that, it gives patients more options and more choice, and hopefully leads to more treatments for other patients in the future.

Q6 What advances have been made in the understanding and treatment of calciphylaxis over the course of your career thus far?

In addition to the evolution from observational to lab-based data, scientists around the world have been busy trying to understand the pathophysiology of vascular calcification as a whole. Vascular calcification can present with coronary artery calcification and cardiovascular disease, or peripheral artery disease calcification, but in skin, it's calciphylaxis. Our understanding of what makes vessels calcify has increased significantly, and there are a whole range of pathways that are involved. We now know it's not just calcium and phosphate getting stuck in the blood vessels, it's actually a process whereby the cells are changing and becoming more bone-like, and depositing calcium and phosphate. We now understand the pathophysiology of vascular calcification far better than we did, which means we have potential targets for therapeutic intervention.

Q7 What further research do you feel is necessary to improve outcomes for patients with calciphylaxis?

Sadly, despite the fact that kidney disease affects so many people, it doesn't have the same degree of research investment as you'd expect, not just in the UK, but globally. Investment into kidney research as a whole is disproportionately low, so we're starting off at a low baseline.

When we get into rare renal diseases, it's even lower. We have looked to cardiovascular research groups to try and help us, but if you think about what happens in cancer and

cardiovascular disease, you have academic centres, and the pharmaceutical industry investing and trying to improve things. I would really like to see industry, as well as policymakers and governments, really prioritising kidney disease research as a whole. We know there's a World Health Organization (WHO) report that has indicated that kidney disease will be the fifth biggest cause of lives lost. We need more investment in kidney research, and then hopefully that will come to rare renal diseases, and looking at pathways and therapeutics that we need to move into trials.

Q8 You are the Rare Disease Group (RDG) Lead for the UK Calciphylaxis Rare Diseases Group. What are the aims of this group, and what does your role as the RDG Lead entail?

The UK has the National Registry of Rare Kidney Diseases (RaDaR). This is an initiative of the UK Kidney Association, which is our professional society, and the UK Renal Registry. The UK Renal Registry collects data from UK renal units every year. This enables us to audit how we're doing, compare against each other, and look for opportunities to improve. The establishment of RaDaR was an opportunity to look at rare diseases across the UK systematically. On the 1st of September 2022, there were over 29,500 UK patients recruited into RaDaR, from 107 sites.

It's huge, and there's nothing like it in the world. RaDaR has various rare disease groups, and calciphylaxis was accepted by the RaDaR group as a rare disease. This allowed us to establish a rare disease group, which I lead. It's made up of doctors, dieticians such as Hewish, and also patients and laboratory scientists. It's an open group for people who have an interest in rare diseases, but specifically for calciphylaxis. Currently, RaDaR for calciphylaxis is being used to collect data and understand the disease burden in the UK, but in the future, it could allow us to find patients and give them an opportunity to participate in trials, and hopefully receive treatments.

Q9 What other rare renal diseases do you think require a greater research focus or increased awareness amongst the wider spectrum of healthcare professionals?

Not just rare diseases, but kidney disease as a whole needs more awareness. Historically, it is poorly taught in medical school, and is sometimes seen as being complicated. It affects a lot of people, so we need to raise awareness, right from medical school, and all the way through training, so that people detect the kidney disease in the first place. That has been our priority nationally, to raise awareness of kidney disease as a whole, whether that be chronic kidney disease that develops slowly, or the acute type (acute kidney injury).

I believe that once we establish a strong foundation in our understanding of common diseases, it's crucial to shine a spotlight on rare diseases as well. These conditions often fall within the realm of nephrology healthcare professionals, given their rarity. However, raising awareness of rare diseases within the nephrology community is a significant step forward. From what I've observed, the renal community in the UK is proactive in considering and addressing rare renal diseases.

The other thing that is helping us identify rare disease is our increasing awareness of the importance of our genes. The UK is a leader in genomic testing, and there is a specific renal section in our UK National genomic test directory.[3] This means that frontline nephrologists can order genetic tests to identify rare diseases, and this is all available within the National Health Service (NHS). I think having early access to genomic testing means we should be able to diagnose patients with certain rare diseases a lot earlier.

Q10 Do you think there is a role for artificial intelligence (AI) in improving earlier diagnosis and awareness of rare renal diseases?

We can't ignore AI, can we? I think the short answer is, there is probably going to be a role for some sort of AI and machine learning in renal medicine.

Research groups are looking into it, but this is harder in rare disease, because AI needs a large amount of data to learn effectively, and rare diseases often lack sufficient data. With this in mind, I suspect AI will largely focus on diseases which have clear characteristics in imaging or pathology. It is still a very early stage for AI in the renal world.

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Q11 To conclude, are there any innovations or developments on the horizon, in either the calciphylaxis or rare renal disease space, that you are excited about?

The way we are delivering trials is exciting. For many years, the standard trial design involved half of the patients receiving a drug, and the other half receiving a placebo, or dummy drug, in placebo-controlled, randomised trials. COVID-19 did teach us the value of doing trials in a slightly different and more pragmatic way, which is really relevant for rare diseases. A good example of a pragmatic trial is a 'platform trial', which enables you to test multiple interventions in a given patient, over a period of time. As something is proven to be effective, it becomes standard care, and is offered to everyone. The platform trial also enables new interventions to be introduced as they become ready for testing. The BEAT-Calci trial[4] is a platform trial that is running in Australia and New Zealand for calciphylaxis, and we hope to be able to bring that to the UK in the future. Sticking with trials, the way we evaluate trials and the endpoints are changing a lot. Again, we're moving towards pragmatic trials that are easier to deliver, but still give us an answer, and I think we'll see more pragmatic calciphylaxis trials in the future. The big development has been the CALCIPHYX trial,[2] which showed us that randomised controlled trials in people with calciphylaxis are possible in the first place.

Transitioning from clinical trials into actual treatments or therapies, we are getting better at broadening our approach from solely relying on medications. In the case of calciphylaxis, recent efforts have explored alternative avenues, such as wound treatments, including topical therapies, and enhancing the efficiency of dialysis itself. It is important to widen our scope beyond medications, and to consider factors like wound care, dialysis optimisation, and even patient-centred aspects, such as pain management, as these directly impact the wellbeing and concerns of patients.

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