CKD of Unknown Origin (CKDu): AKI in disguise?
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Speaker 1:	00:00	Good morning everyone. I want to really thank the organizers for the opportunity to be here. Thank you Ravi for the kind invitation. Today we will be speaking about CKD of unknown origin, which has been also known as Mesoamerican Nephropathy. So when we talk about this disease, we need to know the epidemiology. So these are the first causes of the cases described in El Salvador already a few years back and you can see that they started seeing all these chronic kidney disease and kidney failure of unknown origin.
Speaker 1:	00:45	And the prevalence of chronic kidney disease in Nicaragua. So this is a small city next to León and you can see that by age group, the prevalence of chronic kidney disease is much higher than the prevalence in the United States and this is a compared to the NHANES population. And you can also see that it is actually advanced kidney disease that we are seeing. This is stage four CKD. So when we talk about this disease, there is four things that we need to take into account. So the first geography, this disease happens in Mesoamerican and we have identified other hotspots in Mexico, but it is usually Mexico and Central America. When we talk about a etiology, this is a disease that is not related to hypertension, diabetes, or the typical causes of chronic kidney disease. When we talk about demographics, these are young patients that are mostly male and the disease is occurring between the the third and the fifth decade, and the working conditions are very tough. These patients work in agricultural fields. So we published this paper in looking at the warmest zones in Central America. So you can see here that the warmest zones in Central America correlate very nicely with the site of the epidemic.
Speaker 1:	02:15	So this is the Zafra. These are sugar cane cutters on this population. They work from 5:30 in the morning until exhausted. They get paid by the tonne of sugarcane caught and not by the hour. So we have identified that, this is the new form of slavery. I had the opportunity to visit El Salvador a couple of years ago and this is a ward of, you can see these very young patients dying from kidney failure and basically they come in with end stage kidney disease. They are uremic. They come in, they have a rigid PD Catheter, which you may not heard about

ever, but they have a rigid catheter. They come in, they have 20 or 30 exchanges, and then they are out the door until they are uremic again, the mean survival of these patients is two months. Kidney transplantation is nonexistent in these countries.

Speaker 1: 03:19 So we identified in our center, a very similar population. We actually performed kidney transplants in 52 patients and what we saw is that coming from this area Tierra Blanca Veracruz, which has very similar climate and working conditions of Central America, where we identified these patients that were very young, mostly male, half of them working agricultural workers that are not diabetic, they are hypertensive, but this hypertension we think is secondary to the kidney failure because by the time they come to us, they have a atrophic kidneys and there is nothing we can do. So basically we just do the kidney transplants, but we do not know what they are having the kidney failure from. So then we went ahead and visited this area and we did a prevalence study to see what was going on. So what we found was that a 25 percent prevalence of chronic kidney disease in a very young population. This was general population, the mean age was 40 years old and we found a 25 percent of a chronic kidney disease. So you can see in the green it is a healthy and all the others had some abnormality. This is almost tripled as the data compared by age to the NHANES population.

Speaker 1: 04:44 So what are the potential causes of Mesoamerican Nephropathy? So we think the main cause is dehydration of volume depletion. However, there are other potential causes that we think are lower on the list such as heavy metals, infectious diseases use of NSAIDs, illegal alcohol consumption, and rhabdomyolysis. And we think this dehydration causes repeated tubulointerstitial injury that leads to interstitial fibrosis, tubular atrophy and glomerular sclerosis, all of them causing chronic kidney disease.

Speaker 1: 05:20 So the role of pesticides, we thought a lot about this, however, you know the role of pesticide seems to come lower on the list. These are two studies that showed that in Nicaragua and El Salvador, pesticide was not a significant predictor of the disease and another very elegant study showed that look at urinary NGAL in sugar cane workers and at the end of the harvest. So this is usually in May when the Zafra is done and you can see that the urinary biomarkers go up in sugarcane workers, but that does not happen in pesticide applicators or factory workers. So the role of heat stress, we think is crucial as I sat men work from 5:30 in the morning until exhausted, and after

9:15 in the morning, the occupational safety and Health Administration recommendations would require that workers only work 25 percent of each hour to avoid health risks from heat. So when you look at the symptoms of heat stress and dehydration, you see that they are very nonspecific. You have headache, dried mouth, dysteria, muscle cramps and fever nausea and the harvesters are the ones that experience the more symptoms of dehydration and heat stress when you compare these to the field and plant workers or office workers.

Speaker 1: 06:53 The other characteristic of the disease is that it is common in low altitude regions. So basically if you are a sugarcane worker and live at high altitudes, your risk of having a GFR less than 60 is much less than if you actually work at low altitudes and you are sugarcane worker. And this is the prevalence of individuals with GFR less than 60. Again, you can see how the GFR after nine weeks of clotting actually goes down compared to other professions. So sugarcane workers are at risk of having a decreased GFR.

Speaker 1: 07:37 So what we have been taught so far is that dehydration results in reversible pre-renal AKI. This is what we were taught in medical school, that excessive sweat loss of sodium and water results in pre-renal AKI. And this is totally reversible. However, we know this is no longer true. And these rats were actually forced to be under heat stress, so they were exposed to high temperatures and they were given water. A group of them were given water on the hour and the other group were actually exposed to thermal exposure throughout the day and were only given water at night. So what they saw is that those rats that only got water at night had higher weight loss despite the fact that the total amount of water intake was not different between groups and those serum osmolality on urine osmolality were higher in those that were drinking just water at night. So these translated into having a urinary biomarkers of kidney injury and increased serum creatinine in those rats that were only allowed to drink water at night.

Speaker 1: 08:57 And this also translates into histological damage. So those rats that drink water at night, have much more proximal tubular damage, much more inflammation and fibrosis. So the mechanisms we think are too or 2?. When you have an increasing in the serum osmolality, you have an increase of vasopressin, which vasopressin as I spoke about it yesterday. It is a cause of oxidative stress, inflammation and kidney damage. However, you also have this activation of the polyol or aldose reductase pathway, and in order to have a concentrated medulla , you need to have sorbitol, so when you have an

increased serum osmolality, you increase actually your sorbitol, but then the sorbitol dehydrogenase can convert sorbitol to fructose, and in this last step you have fructose that gets converted to fructokinase through fructokinase to uric acid. So there is a role of endigenous fructose syntheses in thermal, dehydration induced renal damage.

Speaker 1: 10:04 So you can see here in this same experiment. Now you have the knockout for fructokinase, so the same rats get water on the hour versus water at night. But what do you can see is that in the fructokinase knockout mice, those rats had get water at night are prevented from having an increase in serum creatinine and increase in serum NGAL. And this translates into protection from histological damage. So it could be that fructokinase is playing a role and this endogenous fructose synthesis has a role in the disease. So what happens to our population gets rehydrated whith sweetened beverages. So if on top of the hydration you actually rehydrate with sweetened beverage is then we have a problem. And this experiment, that was done in our lab shows how if you are already, you are a rat, that it is already dehydrated and you rehydrate with frutose.

Speaker 1: 11:06 Look at the urine osmolality compared to rehydration with water or Stevia. Same thing for urinary biomarkers, for Lipid peroxidation and for plasma copeptin. Plasma copeptin as I mentioned yesterday, is a marker, a surrogate of vasopressin. So the role of uric acid we think it is also important. So these workers have, we think have rhabdomyolysis due to extreme labor and heat stroke. But this is not a clinical rhabdo, this is a sub clinical rhabdomyolysis. So basically we think that exhaustion and excursion causing rhabdo and causing Hyperuricemia, uric acid crystal deposition could further cause acute kidney injury. So this is a very elegant study conducted in Brazil where you see that, you know, CPK starts off in the morning at 1:09. And then after the day shift it goes up to 386, and look at the serum creatinine before and after the shift, obviously the GFR goes down. So here you see uric acid levels by GFR participants. This is Nicaragua in the blue and this is the NHANES. So you can see that uric acid is much higher and in Nicaragua, workers compared to the NHANES population for the same, level of GFR. And this is an experiment that it was on also in our lab. It is not published yet, but allopurinol and bicarbonate were given to these rats and we had the model of the dehydration hyperuricemia and Rhabdo and you can see that if you actually give allopurinol and bicarbonate, you can actually increase creatinine clearance, decreases serum creatinine. And in my visit to El Salvador, this is what they were doing with the workers. Every time in the morning they would

		get pill of Allopurinol, a little bit of Bicarb on a little bit of an ACE inhibitor, which I was a little anxious about because if you get dehydrated and get put on an ACE inhibitor may not be the best idea.
Speaker 1:	13:26	So putting everything together, we think that dehydration is the main physiopathological pathway which causes an increase, as I said in vasopressin on in the polyol fructokinase pathway. If you add exerting rhabdomyolysis, even if subclinical causing increasing uric acid, right, all this would translate in oxidative stress. Inflammation, endothelial dysfunction, ischemia, tubulointerstitial damage and glomerular damage causing chronic kidney disease. So in conclusion, despite multiple hypotheses, Mesoamerican Nephropathy continues to be a disease of uncertain etiology. Heat stress and dehydration causing repeated episodes of AKI remain the most accepted theory. There is multiple theories, different research groups, different methodologies, and unfortunately politics that have impaired moving the field forward. If this sugarcane workers are caught to be in a research study, they would get fired from the fields. So, it is become very political and very difficult to conduct research in this area. We have joined the CKDu International Working Group and we have established new guidelines for research conduction in this area, which would hopefully change the future and move the field forward. Thank you for your attention.
Speaker 3:	15:14	Thank you professor Madero for your interesting lecture.
Speaker 4:	15:22	Just one quick question or comment. I am of Indian heritage but regratably do not practice in India, but there is a particular state in India from a very similar condition has been described and it is not prevalent in sugarcane workers, but it is seen in people who do manual labor and your hypothesis of persistent subclinical dehydration may play a major role. The disease is known by something else of course. And it is in the State of Andhra in India.
Speaker 1:	15:59	So the difference between the definition, there is a lot of debate between the definition of CKDu versus Mesoamerican Nephropath. So what I described the most is what we see in Central America, but the term CKDu applies obviously to other places because as you said in India, Sri Lanka and we have seen this disease, but we are not sure it is the same thing.
Speaker 3:	16:26	How about is a prevalence of kidney stone in your population?

Speaker 1:	16:30	Very, very small, so I didn't show this, but you do have uric acid crystals at the end of the shift and they describe the symptom, they call shestata which is desyria and they think it is because of uric acid crystals, but the kidney stones per se, we have not seen.
Speaker 2:	16:48	Thank you.
Speaker 1:	16:50	Professor Madero Thank you very much for sharing your data with us.