[MUSIC PLAYING]

MILAGROS SAMANIEGO-PICOTA: We're going to be talking today about the impact of chronic kidney disease in the general population and the way I look at kidney disease in patients with liver disease. There is a discrepancy in the way I approach this problem, compared to some of my colleagues. In my mind, the majority of patients with liver disease also have kidney disease. And this is an area of controversy in the general population.

Now, life sustaining organs, like the lung, the heart, the liver have a very intrinsic, close correlation and interactions with the kidney. We can see it in patients with heart failure. We call it the cardiorenal syndrome. We can see it in patients with liver disease. We call it the hepatorenal syndrome.

And essentially, the impact that the liver has on the kidney function is given by a series of bioactive molecules, hormones, cytokines, et cetera, that change the vasculature or the vasculature characteristics in this system and in the kidney cells, and that leads to the retention of water and salt. That's all there is between the liver and kidney.

Now when I was in training, we all learned about hepatorenal syndrome. Hepatorenal syndrome, the first thing you learn as a nephrology fellow, is not an indication for kidney transplant patient. But the patient that we see today is not the patient with a classical hepatorenal syndrome, or type 1 hepatorenal syndrome, in which the patient does not have any evidence of kidney disease, and that will exclude the presence of protein in the urine or the presence of abnormalities in imaging studies.

And the most common and still the best and cheapest way to image the kidney is the use of a renal ultrasound. And we'll talk a little bit about that later, OK.

Now, in my mind today, the type of patients that I saw when I was a fellow in junior faculty, these were patients with Tylenol poisoning, other kind of drug overdoses, patients that came with fulminant hepatitis A, fulminant hepatitis B. These are not the patients that I have learned to treat as a junior and a more senior faculty.

The patients that I encounter today are patients that have hepatorenal type 2. And hepatorenal type 2 requires consideration for kidney and liver transplant patients, because these are patients that have what we call fixed kidney disease, that is not going to get better once the patient gets transplanted, because kidney disease is always a progressive disease.

You can slow it down, but you will never cure it. You can cure it with a kidney transplant once you can grow a kidney in a Petri dish, but until that happens, the disease will always be slowly progressive.

So this is a figure that I took to from one of Dr. Sharma's papers. It's actually a very informative slide, in which she considers that the risk of the development of chronic kidney disease in patients with liver disease comes from the different situations or pathological insults that the patient can have during the pre liver transplant state, or the development of liver disease. The second head, once the patient has been transplanted, and the third heac is the result of long term, mainly immunosuppression exposure and the side effects of immunosuppression.

Now, I would consider at this stage, that the majority of the patients that I see in clinic at this stage of the pre liver transplant already have some form of kidney disease. And making the diagnosis of kidney disease at this stage is where the difficulty exists.

This is a classical paper. I'm pretty sure you all know about this paper, comes from the University of Michigan, that Akinlolu Ojo published in 2003. It was a paper that utilized registry data, and it was the first paper that really demonstrated that kidney disease were highly prevalent in patients that received non-renal transplants, with patients at greater risk, those receiving in testing, but after that, patients receiving liver transplants.

And you could say-- and this is still questions that we get in the nephrology boards-- that by five years, most liver transplantation, approximately 18% of patients will have some form of kidney disease, and this increases about 28% after 10 years post-transplantation.

And why is that? If you look at the characteristics of the patients that Ojo included in the study, patients had-- if they were a liver transplant recipient-- hypertension, diabetes mellitus, hepatitis C, dialysis before transplantation, which we know, in this day and age, that is a major risk factor acute kidney injury. And need of temporary dialysis is a major risk factor for the development of chronic kidney disease, and diabetes and hypertension being the most common causes of chronic kidney disease in the country, and hepatitis C associated with secondary and primary causes of kidney disease.

Well, this gets a little bit more complicated, and this is where the stress between the nephrologists and hepatologists come from, when it gets down to listing a patient for a kidney and liver transplant. And it's the fact that since the introduction of the MELD score, more patients are receiving kidneys than in the past.

And the classical purist nephrologists will say, well, you are taking this kidney away from a patient that may recover kidney function-- very hard to predict if that will be the case, a priori-- and second, you are taking kidneys away from patients that have kidney disease. It becomes more palatable if you think that the majority of these patients actually have kidney disease, and that unless you gave them a combined transplant, or a combined organ transplant, these patients, the presence of kidney disease itself may lead to the failure and the death of that liver transplant recipient.

And what I just mentioned, you can see in the slide, where since the introduction of the MELD score for organ allocation, the number of kidney-liver transplants has increased substantially. This year, I think we have had about 18 kidney-livers being transplanted at our program, and it seems to be a finding across the state of Michigan.

So there are-- let's just not say that all that nephrologists are wrong. There are some basis in the literature why nephrologists may or may not be hesitant about going with a combined liver transplant. And this is shown here.

These are classical studies that first were published by Bob Wolfe here, where it shows that if you get a diseased donor kidney transplant, your patient with end stage kidney disease, after 106 days, start deriving benefit from that kidney, in terms of morbidity and mortality. But in order to really derive the benefit of survival, the patient has to survive one year.

Now, what happens to the patient that has a kidney and liver transplant? That date, that point in time, increases from 106 days to 244 days. And the way I interpret that data is the way I explain the fellows and the patients.

I need to make sure that when I get you transplanted, you're able to survive 106 days after transplant. Otherwise, if you die-- if you are not able to overcome the risk factors for mortality during those first 106 days, you will die, and there will be not only a damage or an injury to that patient, but also a societal impact to the loss of that graft.

When you're going to give a kidney-liver you need to make sure that individual will survive 244 days. So we need to make sure that the liver recipient that is going to get the kidney has very good options for survival.

So how can we determine kidney disease in your liver transplant recipient? These are clear definitions that were put together by the KDOQI group, sponsored by the National Kidney Foundation-- they are now called the KDO Guidelines, because they are designed for global purposes, as opposed to the United States only, and they haven't changed over the past 14 to 15 years-- which is, anyone with a GFR less than 60 for three months or more has some form of kidney disease, and any patient that has a CKD stage 5 requires dialysis.

Now, how can we diagnose these patients? First thing, you need to document damage for more than three months. So you need to have evidence of pathological abnormalities, in other words, a biopsy, or you need to have more clinically practically cheaper, less morbidity-related markers of kidney disease.

That will be, I don't want to see anyone talking to me without a urinalysis, a urine protein to creatinine ratio. Please don't call me if you don't have an EGFR and at least a BMP on the patient chart.

The imaging test, yes, we're all going to ask you for an ultrasound. But the majority of the patients we end up clearing for a combined kidney-liver, they all have normal ultrasounds, because ultrasound is not the best technique. It's not sensitive enough to determine early chronic kidney disease, or ischemic kidney disease, which is what these patients usually have.

Now, there are all these different stages, and if your patient has an EGFR that is between 60 to 89, I'm pretty sure you will not call me to do an evaluation for a combined kidney-liver. I have followed some of your patients in this stage and all of them have functioning kidneys after receiving a liver transplant alone. You very likely are going to call me around the CKD stage 3, severe advanced CKD stage 3, where the individual has about 30 to 40 ml per minute off glomerular filtration rate.

Now because there is this distress of getting too many kidneys to the liver patients, there are many groups, like O'Riordan and also Pratima that have tried to identify risk factors in patients that require a liver transplant, and may have some level of kidney dysfunction that will require a kidney transplant for survival. And this is just to mention to you that this is Pratima's calculator that can be accessed in this website, where there are many elements of the ones we discuss in the Ojo study. Race, hepatitis C, diabetes, creatinine, the need for dialysis, is put all together in this mathematical equation, to determine what is the risk of the liver transplant patient to develop a kidney disease that will require transplantation.

I have never seen this used in any of the evaluations that we as nephrologists placed in our charts. And I'm trying to see if we can make the new fellows to look at this a little bit differently, and utilize what we ourselves have developed at the university. And this is confirmed, again, when you look at liver transplants.

The majority of candidates for liver transplantation had an EGFR less than 30. They require dialysis, as we mentioned before, and they have all these risk factors also included in the formula that predispose to kidney disease, OK.

So what the first assessment-- we went over that already. The main issue is going to be how we're going to estimate the glomerular filtration rate. Are we going to use a prediction equation, or are we going to use a measurement of the EGFR?

And when we get to prediction equations, there are many types of prediction equations, the most common being the MDRD-4 So there is also an MDRD-6 and a CKD-EPI. So which is the formula utilized at the University of Michigan to report EGFR? Do you guys know? The best, EGFR-MRD-4, OK.

And why it's the best? This is a study from the French that was published about four years ago. I do not know if you are like nephrologists. Nephrologist love the French. So they did an interesting study, which is similar to what the Mayo group in Rochester has done, comparing prediction equations with actually measured kidney function, by using iothalamate.

And one of the things to consider if you're going to tell me your patient has an EGFR of 30 by MDRD-4, you need to be aware that this equation overestimates kidney function in your patient with liver disease. So it's very likely that although it looks 30, it's closer to 25.

So having that concept in mind, this is part of the recommendations that Levitsky and several hepatologists presented as the guidelines for evaluation of kidney disease from the ASB. And one of them is obviously, to utilize the MDRD, or if you want to be more fancy or fancier, the CKD-EPI. For us, the MDRD-4 will work very well for the best assessment of kidney function. There are other methods-- the cystatin C, the iothalamate-- but the majority of programs, including ours, have some difficulties interpreting the GFR measurements that we get with iothalamate, including the Mayo Clinic, where they have perhaps one of the largest experience using this.

In terms of imaging, we talk quite a bit about it, and a message to take home, please don't give gadolinium to any patient that has a GFR less than 30. There is a black box indication, and you may be taken to court if you do that.

So this is a normal ultrasound, what we're seeing here. What we measured is something called, not only the size of the kidney, but the corticomedullary ratio. When a patient has a normal corticomedullary ratio, it looks pretty much like this, thick cortex with some clear definition between cortex and medulla. Then OK, this, the cortex right here, and medulla getting closer to the center of the kidney.

As the kidney becomes sicker, then you can see here that the kidney's smaller. You cannot see that steak-like porterhouse amount of cortex that you see in a normal kidney. And at the same time, there are changes between the density of-- the echodensity of the liver, compared to the echodensity of the kidney. And when there is kidney disease, the kidney always looks more dense than the liver. In normal situations, it's all the way around.

So these are studies that have done kidney biopsies in patients that are candidates for liver transplants or have received a combined kidney-liver. As expected, you will find a series of diagnoses that are linked to kidney disease. Oxalosis, primary oxalosis causes kidney disease, indication for a kidney-liver. There's no doubt about it.

Polycystic kidney disease, same situation. Glomerular disease, most of these patients are going to need a combined kidney-liver, and we can go on and on talking about the different etiologies that combine both kidney and liver disease in our liver transplant candidates.

Acute kidney injury is today, considered a very good predictor of future chronic kidney disease. The majority, or at some point OR patients that are in the hospital status one, will be on some form of acute kidney injury. So the issue is going to be, who is going to recover with a true hepatorenal syndrome type 1, versus the hepatorenal syndrome type 2? And many times, with all these techniques that we have, we cannot really make this diagnosis.

So when I am-- I believe in tissue as the gold standard of diagnosis, OK. And my colleagues will say that my kidney transplants live in pathology, because I biopsy quite aggressively.

We know that patients that get transplants have kidney disease. And this kidney disease may be vascular disease, as shown here, thrombotic microangiopathy, patients with glomerular nephritis. Patients with hepatitis C have a quite common presence of glomerular disease. And this is shown in about 83% of patients with hepatitis C may have some form of immune complex disease, and these may be associated or not to the classical findings of chronic kidney disease in patients with glomerular disease without liver disease

For instance, rheumatoid arth-- factor is common in the majority of patients with glomerular diseases that also have liver disease, but you can also find them in patients that have no kidney disease at the time of biopsy. And this happens mainly because patients with hepatitis C have a disregution of b-cell function, and they also have quite a bit of deficiency of compliment factors, all of which leads to a high risk to develop antibodies.

So who we're going to biopsy? Everybody that's not going to die from the biopsy. That's the most important thing. When are we going to biopsy? The sooner, the better. When the patient is stable, that is the best time to do it. Where are we going to do it? Definitely as an impatient. We can not do these biopsies as outpatient, and in that way, you can have all the blood products and the surgeons online, and make sure that if there is a problem, you can call them.

So which patients I would prefer to biopsy? Patients with hepatitis C-- obviously, this is going to change-- patients that have diabetes mellitus, but do not have microalbuminuria or other findings of diabetic related kidney disease, et cetera.

So these are patients that I took care of years ago are at a different institution, where I biopsied these patients. They all survived, no major bleedings.

So this was a 67-year-old man with end stage liver disease due to hepatitis C, had cryoglobulinemia and poor hypertension and diabetes control, right. You would think that everybody said, oh my goodness, this guy needs a kidney-liver. But no, we needed to biopsy to show that the patient indeed a kidney-liver.

And this is the beautiful biopsy of this patient, that at the time of evaluation had a creatinine of about 1.5, had an EGFR 35 to 30. And you can see how terrible this kidney looks. These are dead gloms. There is a lot of space between the tubules, which means there is either swelling or replacing with scar tissue. And at the same time, you see these infiltrating inflammatory infiltrate, and when you do a special staining-- in this it's called the trichrome staining-- in tricrhome blue is bad. So you can see how good this biopsy looks. It's pretty bad.

So this patient actually, when we look at the gloms that were not sclerosed, even when the patient did not have proteinuria, had quite a severe MPGN type 2. The patient was transplanted, received a liver transplant. Why did the patient didn't get a kidney transplant with all of these findings? Because the patient made urine really good on the OR table.

So the result was-- different situation, please don't go pinpointing my surgeons here. The patient started dialysis in May 2007. We had all the data. So pathology is a pretty good guidance to determine if these guys are going to need a combined kidney-liver, plus these guys had all the clinical markers to indicate that he was going to need it.

Here's another patient, 54, end stage liver disease, comes to be evaluated for the liver transplant, versus a combined kidney-liver. Now, it's 2006, guys. This is 11 years ago when the whole concept of how we were going to make these decisions had started.

So we go and we biopsy the patient again. And this is a trichrome. There is a lot of blue. Blue is bad, OK, even more blue in one of the other cores. And actually, there is almost no vasculature in this gentleman.

Well, he did not get a kidney transplant. He got a liver transplant that on top of that, was complicated by ductopenic rejection, develops chronic kidney disease with many episodes of acute on chronic kidney disease, eventually dies from kidney disease and complications.

So these are the elements that I will recommend for you to refer our patients to us, perhaps hepatitis C. I don't feel as strongly as I did 10 years ago, for obvious reasons.

Advise all your patients who smoke and have liver disease to quit. Tobacco is one of the highest risk factors for the development of kidney disease due to vascular disease. And at the same time, think about referring your patients if they have anemia, bone disease, et cetera, which are things that we nephrologists love to deal with in the outpatient clinic.

So in 2015 at the U, we established a clinic for non-renal transplant patients with CKD. It was an APP led clinic where the protocols were put together by the nurse practitioners and the physician assistants. It was a multi-disciplinary clinic, in which we had not only nursing, but also social work and nutritional expertise and advice, in the development of the protocols and in the care of the patients.

When we did a root cause analysis, trying to find out why patients that had a non-renal transplant were not receiving care by a nephrologist, we find several reasons for that. One was that the patients really, the majority of them, had never been told they had kidney disease, even when you will see, in terms of the distribution of the EGFR, that all of them had kidney disease. There were also the usual problems, the need to have to consult, several practitioners coming to clinic often, et cetera, et cetera.

So we evaluated 89 patients during the first year of operations. 75 patients came from-- were patients who did not have a nephrological follow up. The majority of these patients had CKD stage 3 at the time of evaluation in the clinic. And CKD stage 3 was the highest level of CKD function and stage at the time of referral.

It's good and bad. It's good because CKD stage stage 3 is the time that the patient should be referred to us, because at that time, we can stall the progression of kidney disease. But 35% stayed with us for a couple of months and went immediately to dialysis. So these are the good and bad that we found in these patients.

This-- although, this is a funny story about these this. This abstract was submitted to one of those big awards in patient care improvement at the university, and they were not even selected. And they got the best poster award at the National Kidney Foundation meeting. So I think that the nephrologists were really happy to see this kind of work been done.

So they were able, these nurse practitioners and this team, to improve access of care. They started working in educating these patients, and at the same time, communicating with nurses on physicians.

And the nurses and PAs involved in this clinic had a very high level of job satisfaction-- they preferred to run this clinic than to work with me, helping me in my clinics, which I was very offended about-- in general, had a very low overhead cost, because utilized the existing staff at the time, and was scheduled at times in where the clinic had very low utilization. Imagine Friday afternoons. So that's where the kidney clinic was held.

So unfortunately, it doesn't exist anymore. Hopefully when we get staff, we'll start it again, because we thought we were contributing to the care for patients.

So as a conclusion, kidney disease is highly prevalent among liver transplant candidates and recipients, and, at least, my bias is to see these patients as having kidney disease as well. It is beneficial to identify the risk of developing permanent kidney disease in these patients prior to transplantation, and this can be done utilizing biopsies, evaluating kidney function with measured GFRs or prediction equations, or utilizing the risk calculator developed by Pratima and Bob Merion's group.

The standard assessment of these patients should require referral to nephrology, once the EGFR is 30 or less, before and after transplantation. We are happy to help you out with that.

And even those who had acute kidney injury and recover and just got the liver, send them our way, because AKI is a very high risk factor for the developing of chronic kidney disease. And in general, if you want to be more selective, any patient that had AKI, required dialysis, or has an EGFR equal or less than 30, they are welcome to be referred to our clinics.