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Polycystic Kidney Disease: The Basics Part One of Two



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Moderator:

Lisa Guay-Woodford is an absolute delight to have as a part of our Scientific Advisory Committee. She is a medical doctor at the University of Alabama--Birmingham. She is primarily a pediatric nephrologist, though she has collaborated on other research in ADPKD and also recessive PKD. You will almost always see her name on a journal article, especially about recessive PKD. Not only is she one of the brightest stars on the horizon when it comes to polycystic kidney disease, but she is one of the most delightful individuals you would ever want to meet. I hope you will have a chance to meet her.

She is an Associate Professor of Medicine in the Division of Nephrology at the University of

Alabama at Birmingham. She serves as a pediatric nephrologist at Children's Hospital of Alabama, and she has served as a member of our Scientific Advisory Committee for three years. One of the things you will hear me say is in spite of the fact that we have folks who are well versed and very knowledgeable, we also have some of the absolutely nicest, most gracious people in the world who serve on our Scientific Advisory Committee and come to these events, and you will enjoy getting to know them. Without further ado, I would like to introduce Dr. Guay-Woodford. She is going to do a session on the Basics of PKD, and then we will be on our way. So thanks again for being here.

Dr. Lisa Guay-Woodford

It is a pleasure for me to be here. It is a particular pleasure to be asked to do this talk on the basics of PKD. What I plan to do is to talk to you about the full breadth of polycystic kidney disease. I know most of the people in this audience have autosomal dominant polycystic kidney disease or have a loved one who has autosomal dominant polycystic kidney disease, and most of these loved ones are adults, but ADPKD affects children, as well.

What I am going to talk about is not just ADPKD in adults, but also about ADPKD in children. In addition, I am also going to talk about recessive PKD. There are two reasons for talking about ARPKD to this audience. The first reason is because there are parents in the audience who have children with the recessive form of polycystic kidney disease. The other reason is because we are a community of people who are interested in PKD. That means we are a community of people who should know something about the dominant disease and who should know something about the recessive disease.

As research proceeds, what is becoming increasingly clear is, that lessons from ADPKD actually have applicability for the recessive forms of the disease. And, in fact, the lessons from the recessive forms of the disease, as we will talk about in a minute, actually have implications for the dominant disease. So I think it is important to present this, particularly in a basic talk. I assume that many of you have not been to many of these meetings before, and your knowledge about PKD may be somewhat spotty. So what I am going to do is to try to give you the full breadth. I am going to try to talk about clinical manifestations; I am going to try to put into Reader's Digest synopsis version the recent breakthroughs in terms of the pathophysiology, the mechanisms of disease, some of the genetic advances; and I am going to try to do this for both the dominant disease and for the recessive disease.

00:00

Objectives

- **Review normal anatomy**
- **Discuss ADPKD**
 - ➔ Clinical features - adults
 - ➔ Clinical features - children
 - ➔ Diagnosis
 - ➔ Treatment issues
 - ➔ Genetics
- **Discuss ARPKD**
 - ➔ Clinical features
 - ➔ Genetics
 - ➔ Prenatal diagnosis
- **Perspective**

Outline of this talk

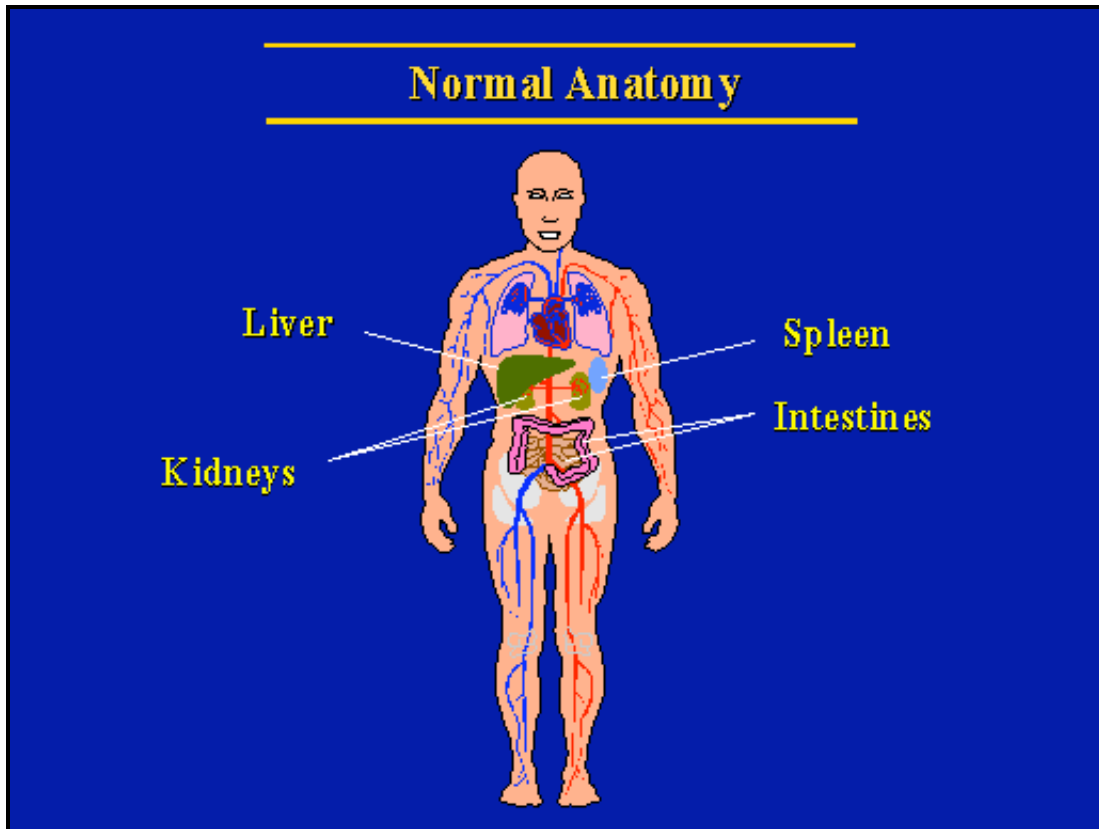
Put in a more specific way, these are the objectives of the talk. I am first going to review normal anatomy. I am really going to start at basics here. A lot of people don't know the road map of the body. Where exactly are the kidneys? Where is the liver and all this other sort of stuff? So we are going to start with that. I am going to talk a little bit about the functioning unit of the kidney and explain a little bit about that.

Then I am going to discuss dominant polycystic kidney disease. I am going to spend a fair amount of time on the clinical features in adults. I am also going to talk about the clinical features in children in a compare and contrast sort of way. I am going to talk about diagnosis, diagnosis as it exists in 1999. I am going to talk about treatment issues, and here I am particularly going to highlight what do we understand about the basic mechanisms of this disease?

Then I am going to spend a little bit of time on the genetic advances in genetic in ADPKD. Dr. Stefan Somlo tomorrow is going to give an advanced course on the genetics of ADPKD. What I want to give you is a sense of what is going on, some of the basic vocabulary, some of the basic concepts so that you may even be able to go to that meeting and get something out of it.

Then I am going to switch gears and talk about the recessive forms of the disease. I am going to talk about the clinical features, where we stand in terms of genetic advances, and the particular issue of prenatal diagnosis. Then I am going to spend the last few minutes just trying to wrap this up and putting it in some perspective. Where are we in 1999?

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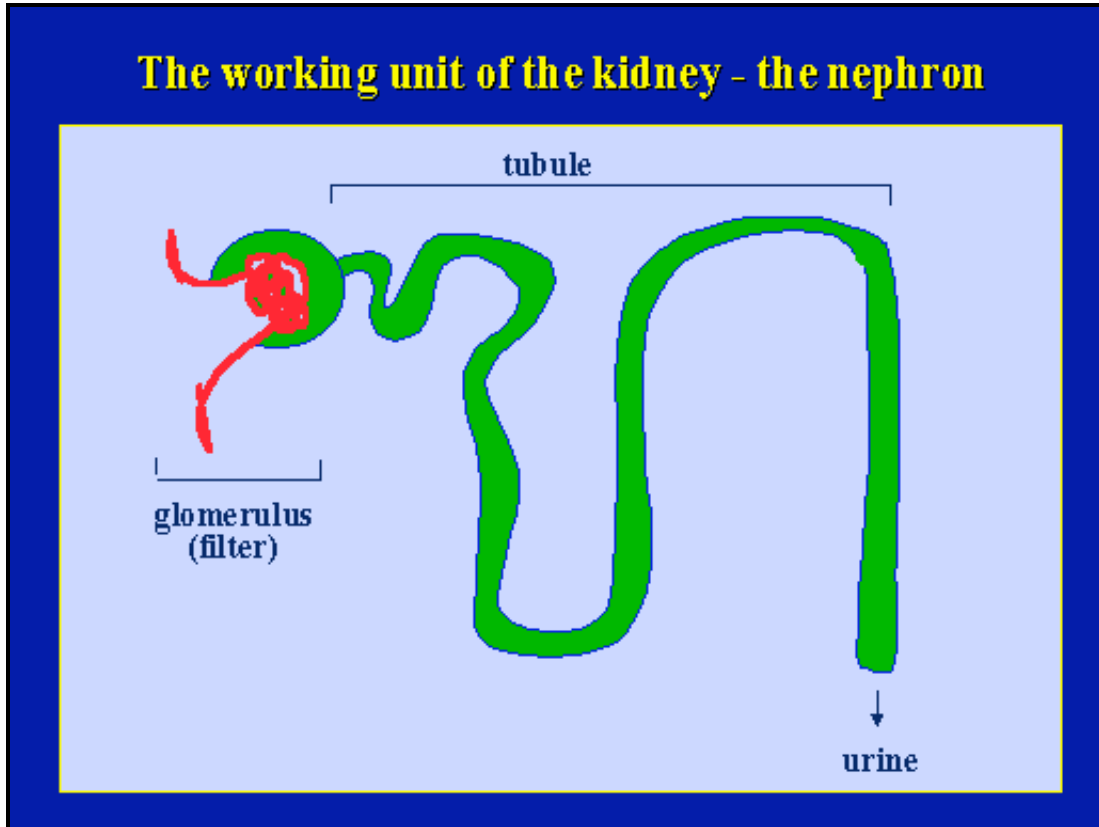


Revie of normal anatomy

Let me begin with normal anatomy. This is my Macintosh version of an androgenous human. The kidneys are here in sort of this greenish color. They sit behind your body, in the back of your body, right here on either side of the spine. The normal kidney size is

about the size of your fist. That is a good rough rule of thumb. In the front of the kidney on the right-hand side is the liver. On the opposite side is the spleen. The liver obviously is important in the dominant form of PKD. The liver and the spleen are important in the recessive form of PKD. Here are the intestines, which also figure prominently in terms of the complications of the dominant form of PKD.

00:00



The nephron: functioning unit of the kidney

This is the functional unit of the kidney. This is called the nephron. The nephron has several components. This is the filtering unit of the nephron, called the glomerulus. Blood comes in here, is filtered across this cup-like structure called Bowman's capsule; extra salt, fluid, and waste products then begin to make their way down the nephron, down the tubule. Additional things are put into this fluid as it makes its way, things that the body wants to get rid of. Sometimes it requires holding on to salts, to calcium, and those sorts of things. Fine tuning of the urinary composition is done here in the collecting duct.

Now there are between, depending upon who you read, 600,000 and a million of these functioning units in each kidney. I should say I purposefully, because this is a basic talk, every slide that I put up here is in your handout. I have left you spaces beside each slide to write down additional things, to write down questions which I will certainly try to answer in detail.

00:00

Clinical Overview: Polycystic Kidney Disease		
	ADPKD	ARPKD
Synonym	adult PKD	infantile PKD
Incidence	1:1,000	1:20,000

Clinical onset	20-40 years; infants/children	perinatal period
Gross pathology	normal-large kidneys	large, uniform kidneys
Kidney cysts	micro and macro entire nephron	1-2 mm; CD
Liver	cysts	portal fibrosis
Systemic disease	yes	no

Clinical overview of polycystic kidney disease

Here is a clinical overview of polycystic kidney disease. The two principle forms are shown on this slide. The dominant form of the disease is also referred to as "adult polycystic kidney disease." But as we will talk about, that is really a misnomer because there are children who can have this disease. Similarly, the recessive form of the disease is sometimes called "infantile PKD", but there are adult patients who have the recessive form of the disease. So it really is more appropriate to use their genetic definition when referring to these diseases: autosomal dominant and autosomal recessive. I will go through what that means precisely in a moment.

Prevalence

In terms of the incidence, ADPKD is very common. This is a rather conservative estimate of 1 in 1,000 individuals. It really comes from the European population, so the white populations from Europe, where the incidence is anywhere between 1 in 400 and 1 in 1,000. Those are the groups who have been studied most extensively. We really don't know the incidence of ADPKD in African Americans, in African populations, in Asian populations, and in some of the other ethnic groups in the world. That is just not known. So this number, you should realize, refers to the incidence in the white population.

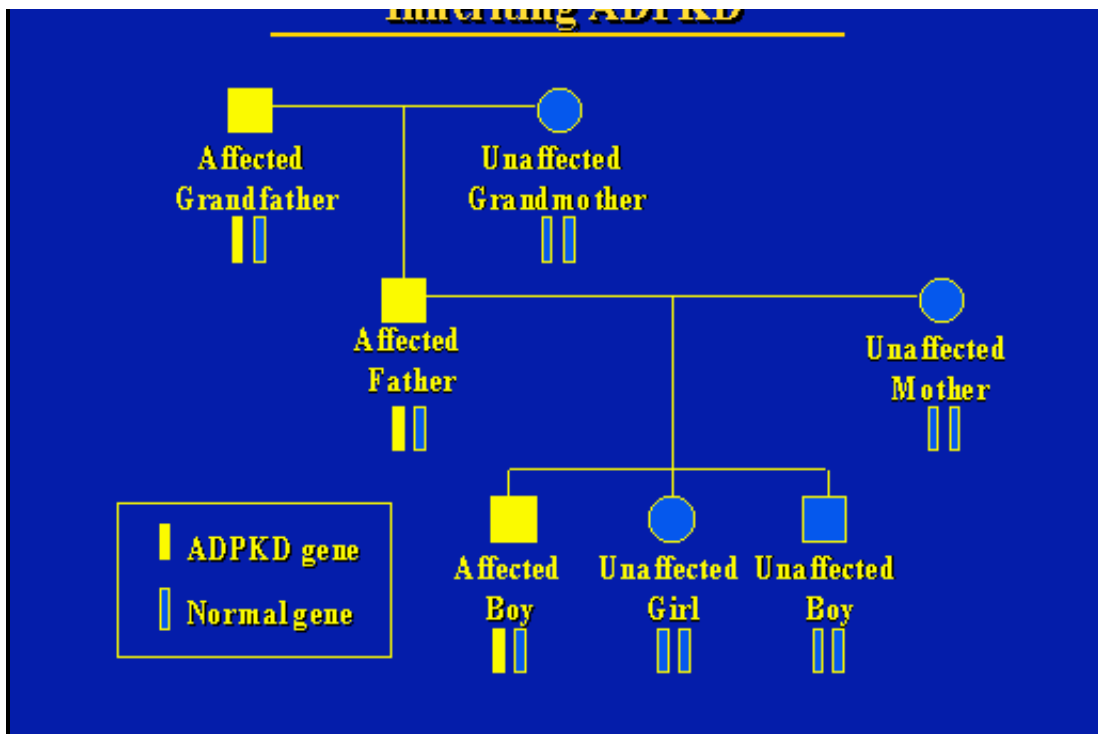
Age of onset

The clinical onset in ADPKD is typically in the third to the fifth decade of life, your 20s or your 40s. However, there is a subset of patients who present either as infants, even in the newborn period, or as children. As I said, we will talk about that. The gross pathology when you just look at the kidney, sometimes it can be normal in size, particularly when you still have normal renal function. But very often it is very large in size. These cysts can occur anywhere along the nephron length, as we will talk about in a minute. The liver is involved in ADPKD with cystic changes. That primarily happens in adults, and there are a number of systemic manifestations. What I mean by that is that there are a number of organ systems that are involved in this disease. This is not just a kidney disease; it is a systemic disease. We will go through that in some detail.

ARPKD vs. ADPKD

In comparison, ARPKD is much less common. It primarily shows up in newborn children. The kidneys are large, and they really keep their kidney shape, their kidney bean shape is really preserved. They have very small cysts. Those cysts tend to be confined to one specific area of the nephron for reasons that we don't understand at all. The liver lesion is quite different. It involves a fibrosis or a scarring of the biliary area of the liver. This is a disease that primarily, if not exclusive, effects the kidney and the liver. It is not a systemic disease.

00:00



Inheritance of ADPKD

Let's talk a little bit about inherited ADPKD. As a pediatric nephrologist, I see families with both ADPKD and ARPDK. People are often confused. There is all this thing about skipping generations and sixth cousins removed and all of this nonsense. So what I want to do is to take you through what does it mean for a disease to be transmitted as a dominant trait? And what that means is that it is transmitted from generation to generation.

Now for an autosomal dominant disease, the sine qua non, the absolute marker of an autosomal dominant disease is father to son transmission. In autosomal dominant polycystic kidney disease, the gene can be transmitted to every generation. The way this works is we have probably somewhere between 50 and 100,000 genes in our body. The current estimate is something around 80,000. Each of those genes comes in two copies. Those copies when a new child is made, one copy comes from the father, and one copy comes from the mother. It is an entirely random event. You have absolutely no control how this can happen.

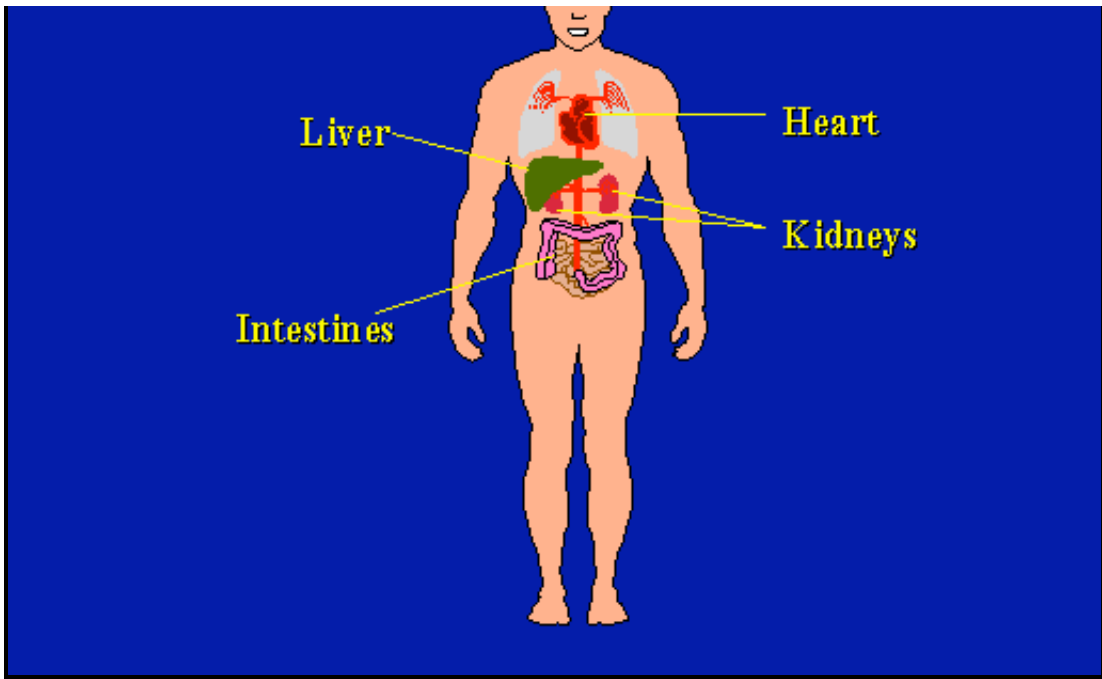
Risk of transmission of an autosomal dominantly inherited disease

If you have an autosomal dominant disease, what it means is one of your copies has a disease in it or has a mutation in it. So your child has a 50 percent chance of getting this copy or this copy. Therefore, for every pregnancy, every child is at 50 percent risk of inheriting the disease gene. This IS an entirely random event. You could have six children and none could have it. You could have six children, and because every child is at 50 percent risk, you could have six children with the disease. It is an entirely random event. It is not something you can control at all.

I think it is a very important thing to stress because when I see parents who have children with this disease, there is a tremendous sense of guilt. As a parent, of course I understand that. But there is nothing that you can do about it, and I really want to emphasize that to this group because in my clinical practice, that has been a source of some confusion and perhaps some unnecessary guilt.

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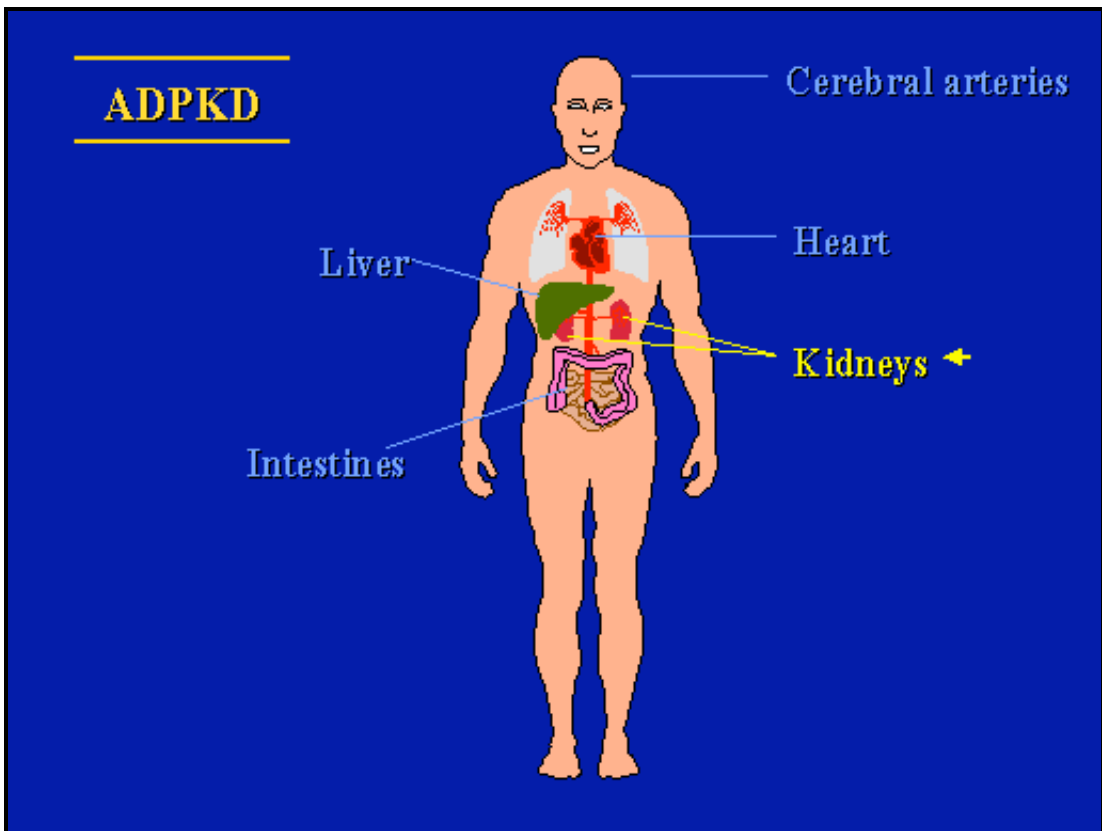




Systemic nature of ADPKD

So ADPKD, as I said, is a systemic disease. It involves multiple organs. Obviously the kidneys are a major focus of our attention. The liver, outside of the kidneys, is another major source of complications for dominant polycystic kidney disease. The heart, as we will discuss; the arteries of the head; and finally the intestines--these are the major sites of complications of ADPKD.

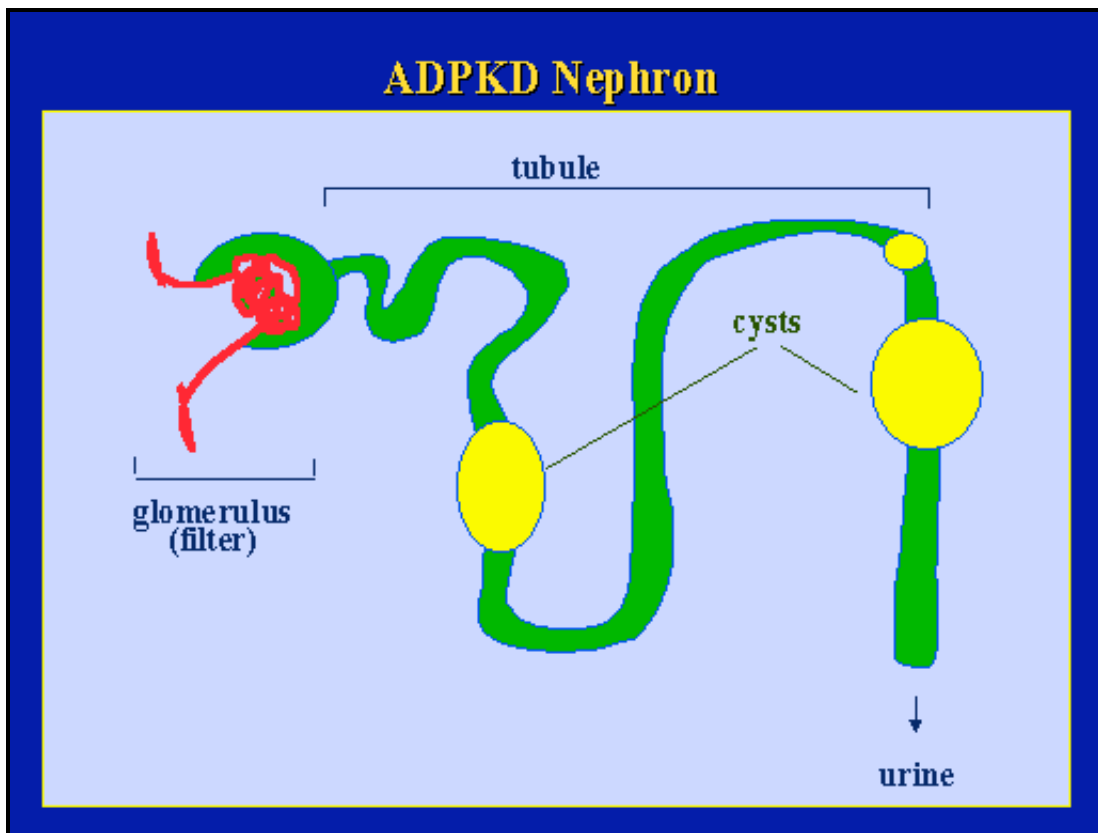
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Effect of ADPKD on the kidneys

So we are going to start with the kidneys. Here I want to go to the ADPKD nephron.

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The nephron and how it is affected by ADPKD

As I said, cystic structures can arise anywhere along the nephron length. What is very interesting about ADPKD, and I want to plant this seed for you and we will come back to it later, is only between 1 and 5 percent of those million nephrons are involved with cystic change. So this is an amazingly aggressive disease mediated by basically bullies that seem to destroy the rest of the normal kidney. We will talk about how is this the case.

00:00

Kidney Complications

- | | |
|---------------------------|----------------------|
| 1. Hypertension | 60-100% |
| 2. Gross hematuria | 50% |
| 3. Infection | common |
| 4. Kidney stones | 20-25% |
| 5. Kidney failure | 50% by age 60 |

Renal complications of ADPKD

Hypertension

In terms of the kidney complications, hypertension is the most common complication. Sixty percent of patients who have normal kidney function still have hypertension. And we are going to talk in some detail about what that means. Perhaps as high as 100 percent of patients who have gone on to lose a substantial portion of their kidney function have hypertension.

Gross hematuria

What that means is blood that is visible in the urine. This occurs in a large number of patients who have ADPKD. The urine can be either red, it can look like cranberry juice, or it can be a darker color, sort of like tea. But clearly the color of the urine has changed. I should point out that there also is the possibility of having a little bit of blood in the urine that you can't see. It's not visible to you, but you can pick it up under a microscope. And that is called, in comparison, microscopic hematuria.

Infection

Infection is very common in ADPKD. The precise incidence or the precise prevalence of infection is not a number that we know. However, some authors have written that as many as 50 percent of patients during the course of their time with ADPKD will develop a symptomatic urinary tract infection. We will talk a little bit about the sites of that infection.

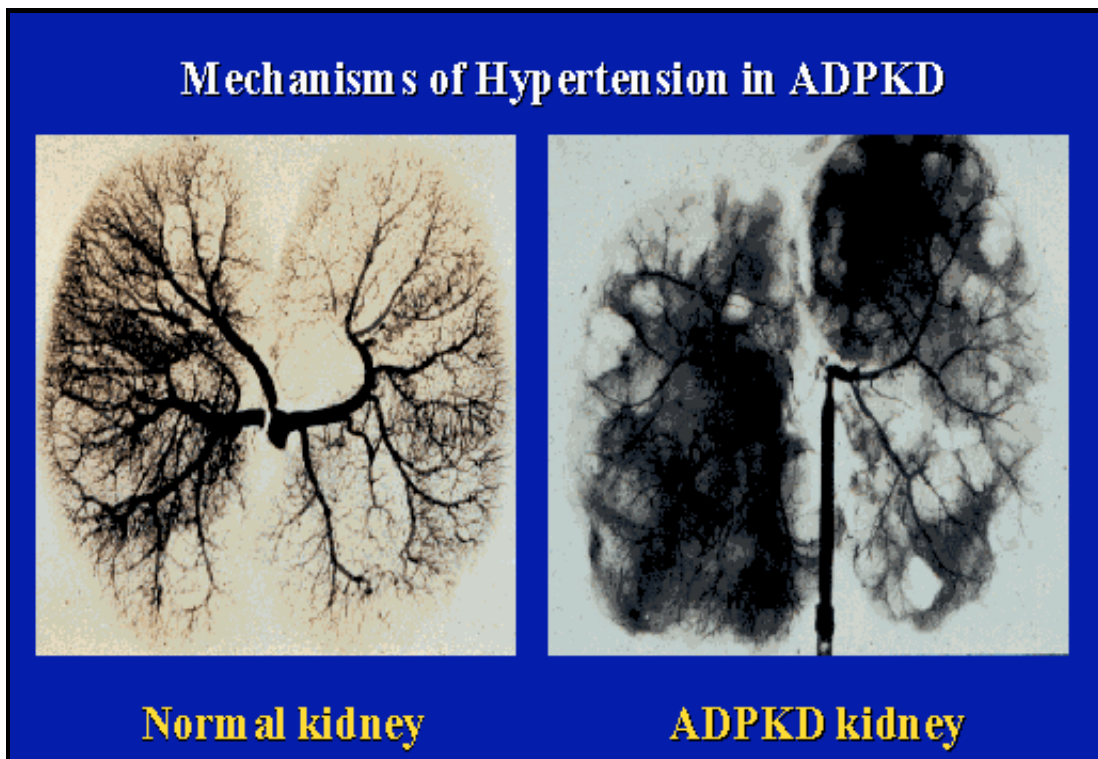
Kidney stones

Very common in ADPKD. We will talk a little bit about what the basis for that is.

Kidney failure

Finally, obviously the most feared consequence of kidney involvement in ADPKD is kidney failure. But, again, it is not 100 percent. The current estimate is that 50 percent of people will go on to develop end-stage renal disease or will require renal replacement therapy, be that dialysis or renal transplantation, by the time they're 60 years of age. A very interesting statistic, but perhaps just as interesting is what is the story with the 50 percent who haven't gone on to end-stage renal disease? And is there something that we can learn from them about the pathogenesis of the disease?

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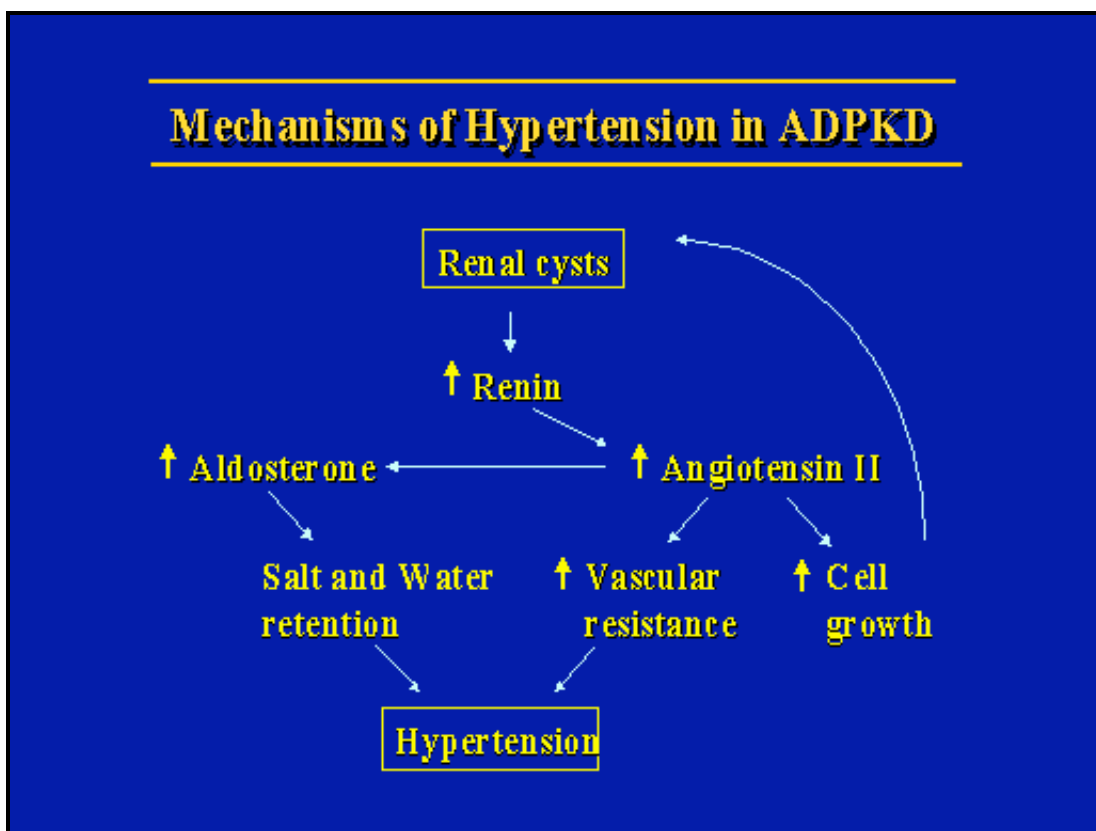


Why hypertension occurs in ADPKD

I think this slide is very helpful in understanding hypertension. I wanted to take you through this. On the left-hand side of the slide is a normal kidney. You can see the kidney bean shape here. The reason this kidney shows up is that there is a contrast agent that has been put in to the major blood vessel, the aorta here, and that has made its way into the renal arteries, to the major blood vessels that are supplying the kidney. You can see that there is a nice tree-like or arborization of these blood vessels that are basically supplying all of the different regions of this kidney bean structure.

On the right-hand side of the slide is the same sort of study done in kidney that has ADPKD. What you can pick out here is that it doesn't look like there are any blood vessels at all. In fact, in this portion of the slide, if you will, the tree has been pruned. The blood vessels are really less prominent. This probably is one of the major mechanisms of hypertension in ADPKD.

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How renal compression and scarring result in hypertension

That is discussed on the following slide. The renal cysts, for a variety of reasons, some of which involve physical compression, some of which involve inciting a scarring reaction in the kidney, and there are probably other reasons as well, seem to squish the blood vessels and seem to alter the blood supply of the kidney. When the kidney doesn't receive enough blood, it releases a hormone called renin. Renin, in turn, stimulates the production of a very powerful substance called angiotensin II.

Angiotensin II has two major functions in the body. The first is it increases vascular resistance. In other words, it takes a blood vessel and makes it squeeze down. The purpose of that is to raise blood pressure. This is a normal mechanism to raise blood pressure. But the other thing that angiotensin does is it stimulates cell growth. So in the context of ADPKD, both of these situations are probably very important. Increasing vascular resistance increases the tone in the blood vessels and raises the blood pressure. This

stimulus to increase cell growth may in fact feed back, as we will talk about in a little bit, and stimulate more growth of cysts. In addition to these two functions, angiotensin II stimulates the production of a powerful salt-retaining hormone called aldosterone. Aldosterone tells the kidney, "Hold on to salt and water." So in addition to the blood pressure going up because the blood vessels are squeezing, there is more fluid in the tank because the kidney has held on to salt and water, and that results in high blood pressure.

Role of angiotensin converting enzyme (ACE) inhibitors

Many of you are probably taking an angiotensin-converting enzyme inhibitor, an ACE inhibitor: captopril, enalapril, lisinopril, quinapril--I think probably are somewhat common names to many of you. Those agents block this ability of renin to stimulate angiotensin II production. As you can see, that is a very good place to start in dealing with the hypertension associated with ADPKD. Others of you may also be taking a calcium channel blocker. What a calcium channel blocker does is it tells the blood vessels, "Hey, chill out. Relax." It decreases their vascular resistance. So in combination, an angiotensin-converting enzyme inhibitor and a calcium channel blocker can decrease that vascular resistance that leads to high blood pressure.

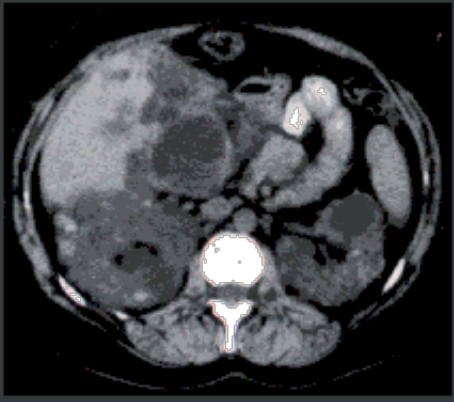
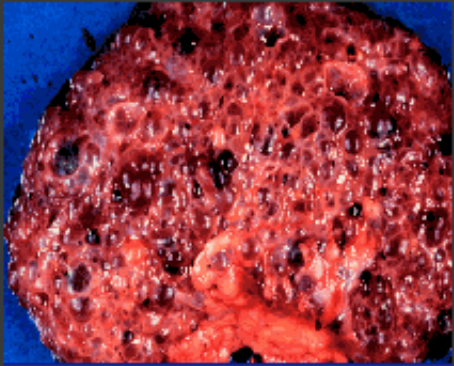
Importance of a low salt diet

The other thing many of you may have been counselled by your physicians is, "Don't go hog wild eating salt." The reason is because the situation in the kidney is naturally tuned in ADPKD for salt and water retention. So if you will, it is like you are always primed to be eating Chinese food. You know how you feel after you've eaten Chinese food--your rings don't quite fit and you feel just a little bit bloated. The reason for that is that you've held on to extra salt because many of the things that we use to make Chinese food are very, very high in salt. In ADPKD, you run the risk of always being a little bit salt overloaded. So if you have a diet that is high in salt, you are kind of feeding into this vicious cycle that causes hypertension. For this reason, some of you may be taking diuretics or water pills as well. I hope this schema helps you understand why your physicians have chosen the various therapeutic interventions that they have chosen.

00:00

Cyst Complications

1. Hypertension
2. Gross hematuria
3. Infection
4. Kidney stones
5. Kidney failure



Cyst complications

Let's talk a little bit about cyst complications. I tried to be as delicate as possible in showing a picture of an ADPKD kidney. I like the red, so I picked this one. This is an ADPKD kidney, and all of these black areas here are cysts.

Now if you look with an imaging study, those cysts show up here as a little bit different than the substance of the kidney otherwise. This is a CT scan. And many of you may have had CT scans. Basically the image of a CT scan is the patient's feet would be out here in the room and their head would be behind the blackboard. This is a slice through the body. These are the kidneys lying right beside the spine on either side. This is a cyst in a patient with polycystic kidney disease. This is the liver. You can see the liver also has cysts.

Hemorrhage

When I talk about cyst complications, here I wanted to digress a bit to include the liver as well because the cysts in the kidney can bleed, and sometimes that causes pain; but sometimes that blood can get to the outside of the body via the urine, and you can end up with gross hematuria. The cysts in the liver can bleed. It is not quite as common, and that can cause pain. And it is pain primarily felt in the right upper quadrant.

Infection

In both situations, cysts can get infected. It is much more common for infection to involve the cysts of the kidney, but cyst infections can be a problem in both the kidney and in the liver. So if you develop a fever and you have either back pain or flank pain that is new or more severe in intensity or if you have right upper quadrant pain, it is very important for you to call your physician because you have a situation that is different from the general population. You have cysts, and those cysts can be infected. If infected, that needs to be addressed in a very expedient way.

Kidney stones

Let me just make a quick aside about kidney stones. The basis for kidney stones is not really well understood in ADPKD. Many of them contain calcium. Some of them contain a substance called urate, which comes from uric acid. It is a normal break-down product, for example white blood cells in the body. There seems to be a higher level of uric acid in the urine of ADPKD patients, for reasons we really don't understand. But if you couple that with the fact that as the fluid makes its way through the nephron, it's going a little bit more slowly than in someone who has entirely normal kidney function. And the level of acid in that urine is perhaps a little bit lower. That uric acid can come out as crystals and form stones. And if you have too much calcium in your urine, because people with ADPKD don't also put enough citrate into their urine that can kind of buffer that calcium, you can also form calcium stones. So with sharp, sudden-onset pain--you should ask yourself "Could I have a kidney stone?"

00:00

Kidney Failure (ESRD) in ADPKD

USRDS Statistics for 1996:

- 13,454 ADPKD patients were treated for ESRD (~5% of the total ESRD population).
- 1,796 ADPKD patients entered ESRD.

- The cost of renal replacement therapy for ADPKD patients exceeded 1 billion dollars.

Kidney failure

Let's talk a little bit about kidney failure. As I mentioned, this is the most feared consequence of ADPKD. These statistics are from a national database called the USRDS, the United States Renal Disease Study. These statistics are most recently available for the year 1996. What I want to point out to you is 13,000 patients with ADPKD were treated for end-stage renal disease in 1996. That is 5 percent of the total ESRD population. Hypertension and diabetes cause more ESRD than PKD, but PKD is third or fourth on the list. In that year alone, almost 1,800 patients began treatment for end-stage renal disease.

The cost of renal replacement therapy for ADPKD patients just by themselves in that year exceeded \$1 billion. So when you talk to your Congressman, as I know Dan and Tim and Tonya have all pleaded with you to do, one of the things that often gets the attention of people in Washington is the cost. Please pay attention to this number and use it liberally.

00:00

Fixed risk factors which accelerate loss of kidney function

Factor	Association
• Male gender	yes
• African American	yes
• Structural factors	yes

Fixed risk factors for progression of renal disease in ADPKD

Factors which accelerate the loss of kidney function. On this slide I listed the factors that you cannot do anything about. There is information in the literature to suggest that being a male with PKD, you have a risk of progressing more quickly to end-stage renal disease, but clearly your gender is not anything that you can do anything about. Similarly, race is not something you can do anything about. There is evidence, and it is much less convincing evidence, but there is evidence, including from our own institution in the study that we've just recently completed, that suggests like many other kidney diseases, ADPKD has a more accelerated course in African Americans. We don't really understand the basis for this in ADPKD or, if the truth be told, in most other renal diseases. These are just basically

observations. The final thing that you really can't do very much about is the severity of the structural involvement. How big are your kidneys? How big are the cysts? these factors seem to portend a more accelerated disease course.

00:00

Modifiable risk factors which accelerate loss of kidney function	
Factor	Association
• Hypertension	yes
• Gross hematuria	yes
• Urinary tract infection	+/- (males)
• Pregnancy Number	+/-
• Diet	?

Modifiable risk factors in ADPKD

The factors that you can do something about are listed on this slide.

- **Hypertension, untreated hypertension** -- I think there is very good evidence now suggesting that it accelerates the progression of polycystic kidney disease. So we should all be very vigilant about controlling blood pressure in PKD patients.
- **Gross hematuria** -- multiple episodes of gross hematuria also seem to be associated with a more accelerated disease progression. You could say, "Well, there is not really very much you can do about it." Well, in a sense there isn't, but in a sense there is. For example, sports that involve blunt trauma, football, for example. I live in the Deep South. Football is a passion there. I strongly encourage my ADPKD kids to play soccer, play baseball. Play a sport, but don't play one that you can get blunt trauma and precipitate gross hematuria.
- **Urinary tract infection**, particularly in males, seems to be associated with a more accelerated disease course. That is probably because in general urinary tract infections are pretty common in women. But most women who have urinary tract infections, whether they have ADPKD or not, those urinary tract infections tend to involve the bladder. So it is a little more difficult to tease that apart in women. When men with ADPKD get urinary tract infections, they either involve the substance of the kidney or they involve the cysts themselves. So that seems to be associated with more significant progression of disease.
- **Pregnancy number**
-- This is a question that gets asked a lot--pregnancy number. And we will talk about pregnancy in just a minute. But pregnancy number is sort of plus/minus because the data in the literature are somewhat conflicting. In sorting it through, I think this is the bottom line. The bottom line is pregnancy number if you have normal blood pressure probably doesn't make a difference. It may set you up for developing high blood pressure, but it doesn't make a difference in terms of your ultimate progression of

disease.

If, however, you have hypertension, pregnancy number is directly correlated with more aggressive disease. In other words, if you have three or more pregnancies and you are a hypertensive woman, you probably will have more accelerated PKD, progression of your PKD, than if you had fewer pregnancies. And I think that is an important thing as we physicians counsel you as patients about your life decisions.

- **Diet**

-- I know this is a topic that many of you are very, very interested in because quite frankly it is so easy and you can control it. Does diet play a role in the progression of ADPKD? I think the short answer is that the jury is still out. The studies that have been done in humans say no.

But if you look more closely at those studies, including a very big study that was done in the United States called the MDRD Study, the patients who were enrolled in that study generally had lost a fair amount of their kidney function already, and many of them were hypertensive. That study said it didn't matter how much protein you ate or how much phosphorus you had in your diet or how hypertensive you were. But that is probably not the group that we really wanted to study. So the data in humans is not clear.

However, there are multiple animal models of polycystic kidney disease. Mice and rats are the most studied, but there are Springbok deer that can get PKD. There are Persian cats that can get PKD. It is a lot easier to work with mice and rats. In those animal models, there is some very compelling evidence that potassium citrate is a very helpful thing in slowing the course of the disease. In other animal studies that the kind of dietary protein is important. A diet high in soy-based protein is better than a diet of animal-based protein is slows the disease course in some mice with PKD.

So if you say to me as a physician, particularly as a pediatrician, "Well, should I put all my family on soy protein?" What I would say to you is, "Pick something that is potentially helpful but that will do no harm." Remember that maximum medicine is above all "do no harm". This is one of those situations. If you are working towards having more soy-based protein in your diet, like tofu, I don't think it would hurt you. There is evidence from animal models, if we can extend it, that suggest that it might be helpful. Do I think that in the next session, in the year 2000, that we should serve only tofu lasagna? No, I don't think there is any data to support that.

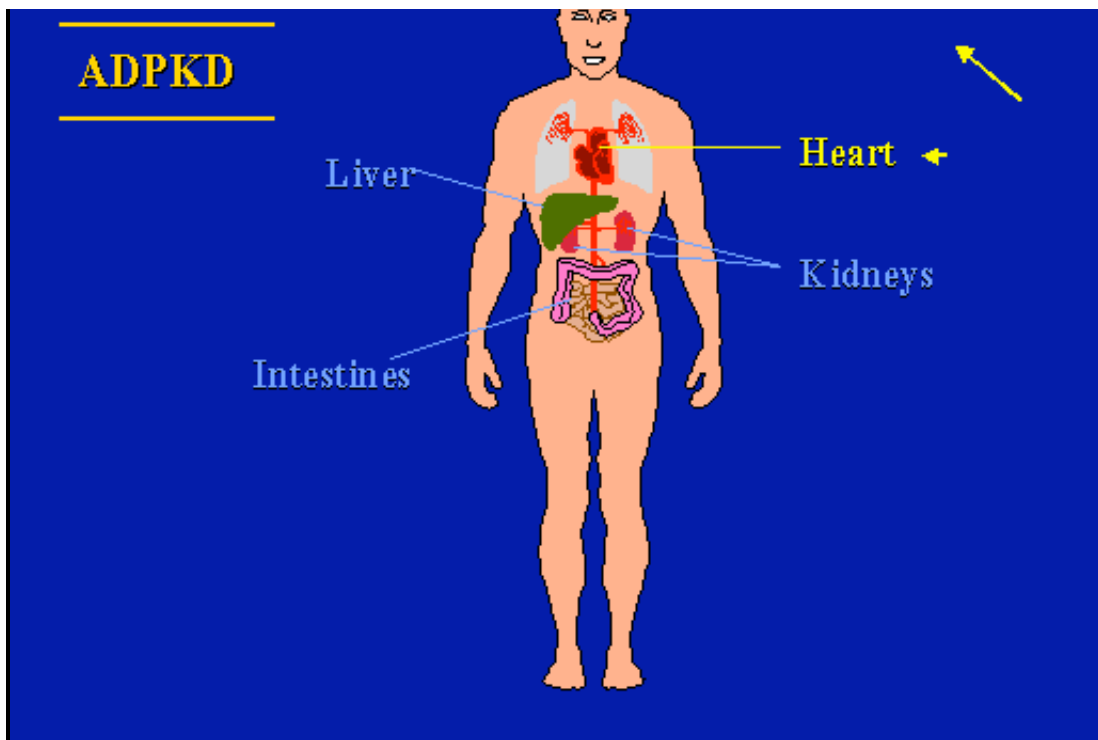
I do think that you have to be very careful in choosing what you do. Use a fair amount of common sense as you make these choices. I will tell you, and I will emphasize this again, that Dr. Arlene Chapman and Dr. George Tanner will be talking about diet in PKD in one of tomorrow's break-out sessions. So for those of you who are really interested, I suggest that you think about that.

Role of alternative medicine

Let me use this as a jumping off point for one more comment. I think that we who do traditional medicine have... most of us, the lion's share of us... have the best of motivations and we try very hard to have the best information, but we don't have all the answers. Many of you with chronic diseases search in other places for helpful things, helpful additions to your treatment. I don't think that is wrong. In fact, I think it is a very good thing for you to take control of your PKD, on the one hand. On the other hand, please be careful. Please be careful about herbal medicines. Please be careful about other things. Discuss these other alternatives with your physician. Partner with your physician. Investigate what the possibilities are so that you make good choices that above all do no harm.

00:00





Vascular disease associated with ADPKD

Let's leave the kidney and go to the vascular circulation. Although the issue of aneurysms is talked about a great deal, it is not one of the most common complications of ADPKD. I chose to talk about this next because cardiovascular disease is the single most important cause of death in ADPKD patients. It has many factors that contribute. Hypertension certainly is one of those factors. In fact, it is a major factor. So, again, I would caution you. Please be scrupulous about trying to control your blood pressure.

00:00

Cardiovascular Complications

- 1. Intracranial aneurysms 10-15% of families**
- 2. Other aneurysms rare**
- 3. Cardiovascular disease common**
- 4. Heart valve problems 20%**

Intracranial aneurysms

Let's first go to one of the very feared complications of ADPKD, and that is intracranial aneurysms. If you take the whole cohort of ADPKD patients, and again this is primarily people of Northern European decent, 10 percent of patients will have intracranial aneurysms. There is a family history of intracranial aneurysms. What that means is that intracranial aneurysms tend to cluster in families. That will become important as we think about how do we screen for this problem. Other aneurysms involving the aorta, for example, the major blood vessel that leads from the heart to the rest of the body are rare. Cardiovascular disease we have talked about.

Heart valve problems -- mitral valve prolapse

Can I just ask for a show of hands? How many people in this room have an unusual chest pain and they feel their heart beating in their chest fast? Palpitations is what we call it. If you could just put your hands up. Okay. Now I am no whiz at math, but that is a little bit less than 20 percent. About 20 percent of adults with ADPKD have what is called mitral valve prolapse. The mitral valve leads from the chamber that receives blood from the lungs, on the left side, called the left atrium, leaves from that chamber to the left ventricle. That is the chamber that pumps blood to the body. That valve is like a door. It is almost as if the door was a rubber door and was kind of just floppy. It doesn't close precisely. So when that left pumping chamber contracts to send blood to the body, some of it heads back to the receiving chamber for the lung. That is called mitral valve prolapse. For reasons we don't understand, the incidence of mitral valve prolapse is higher in ADPKD patients, and also these patients tend to be more symptomatic than their colleagues or their compatriots who have mitral valve prolapse and who don't have ADPKD. It is more common for them to have palpitations and atypical chest pain.

The reason I point this out to you is, remember, I just told you cardiovascular disease is a major cause of death in ADPKD. So if you have chest pain, be sure you talk to your physician. Don't just dismiss it to, "Oh, it's my mitral valve prolapse." Be sure you have mitral valve prolapse. Be sure the pain is consistent with mitral valve prolapse and not with angina or ischemic heart disease, too little blood flow to the heart.

00:00

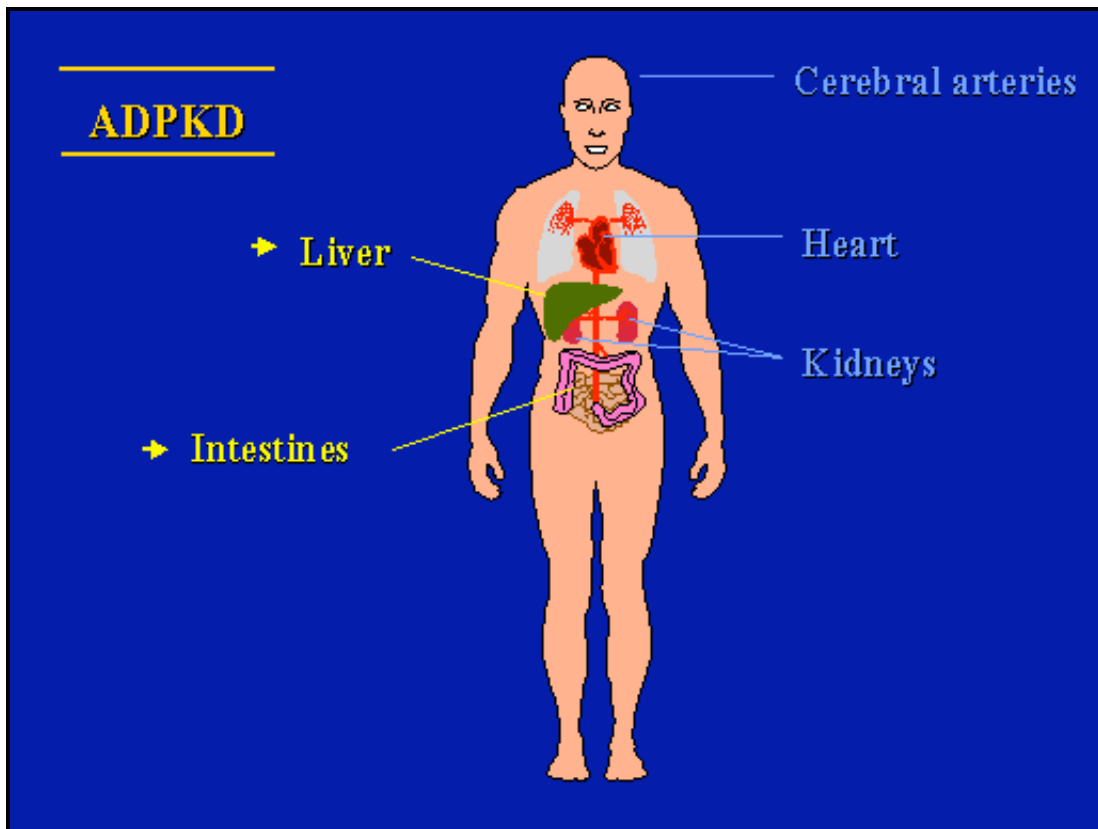


Intracranial aneurysm

Intracranial aneurysms

Now this is a picture to show you what an intracranial aneurysm looks like. This is dye that is put into the arterial system. We are going to follow the dye from here all the way around to here. You see there is kind of a little bubble, right there. That is an aneurysm. They can be very small. But a clinically significant aneurysm is about 6 mm. Now for those of us in the United States who completely refuse to do anything with the metric system, let me tell you 6 mm is about a quarter of an inch. That is not very big. The way that we think about doing something, screening people, thinking about intervention for intracranial aneurysms is as follows. We borrow heavily from the normal population. We really don't understand in great detail the natural history of intracranial aneurysms in ADPKD. We know that about 10 percent of patients with ADPKD have intracranial aneurysms. In comparison, about 2 percent of the general population. And we also know that ADPKD families can have a clustering of intracranial aneurysms. So this is the consensus that has emerged. If you have someone who is basically healthy, between 18 and 35, who comes from a family that has a history of intracranial aneurysms, you screen them by doing what is called a magnetic resonance angiography or MRA. If they have no evidence of any intracranial aneurysms, you screen them again in five years and at five year intervals until they age beyond beyond 35 YEARS. If they have an aneurysm that is less than a quarter of inch in size, you screen them again in two years. If it is greater than a quarter of an inch in size, you proceed to a neurosurgical consultation. People get very worried about this. They say, "I have had a headache. Shouldn't we be doing a study?" Well, you certainly should be paying attention to the headaches. So a severe, sudden onset... you feel your head is going to blow off kind of headache should not be taken lightly, particularly if it increases in intensity, and particularly if you start to notice you are smelling something funny, you are losing sensation in your hands or in your feet, you're slurring your speech--those are neurologic signs. You need to call your doctor immediately.

00:00



Gastrointestinal and liver complications associated with ADPKD

So let's leave the brain and go to the liver. The liver actually, aside from the kidney, is the most common source of complications in ADPKD.

00:00

Liver/GI Complications

1. Liver cysts

asymptomatic

up to 80%

symptomatic

uncommon (W:M 10:1)

2. Pancreatic cysts

~10%

3. Intestinal diverticuli

~80% pts with ESRD

4. Hernias

~10%

Liver cysts

In fact, asymptomatic cysts in the liver occur in about 80 percent of people. So if we screened everybody in this room who has ADPKD, the vast majority of you would have evidence for cysts in your liver, but most of you would feel perfectly fine and have no problem. There is a subset of patients who have symptomatic cystic liver disease. Those patients overwhelmingly tend to be women, for reasons we will discuss in just a moment.

Pancreatic cysts

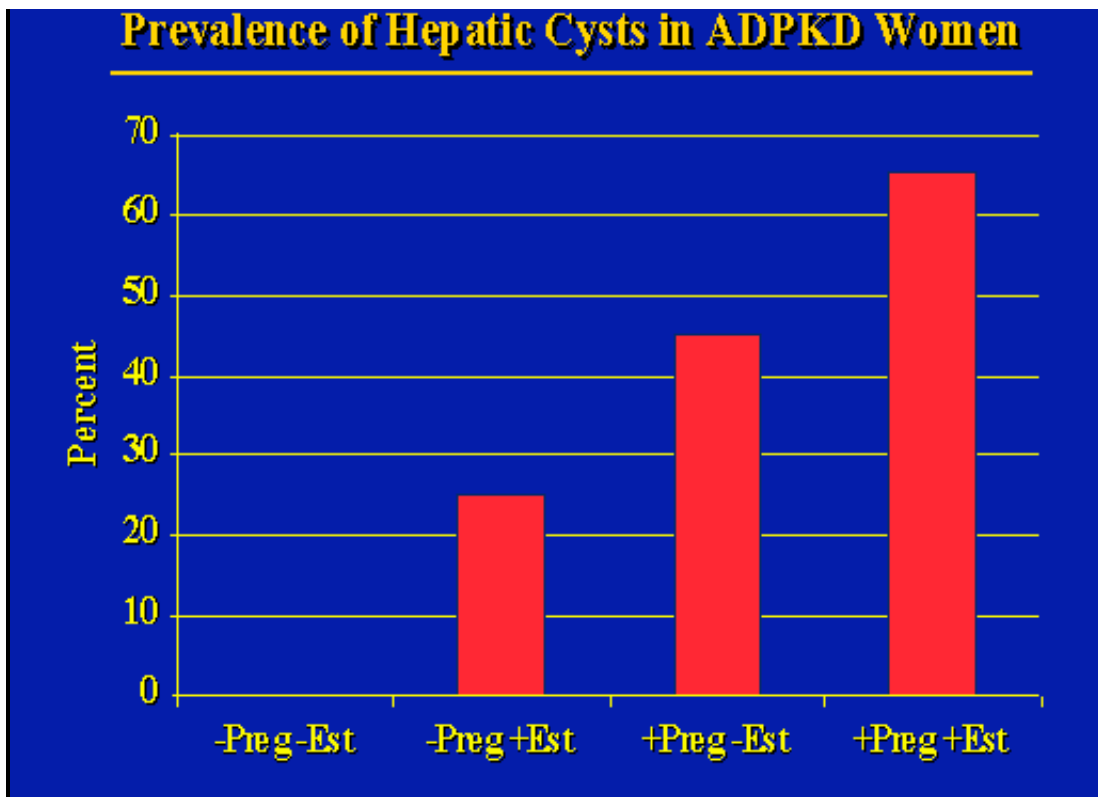
Pancreatic cysts do occur in ADPKD in about 10 percent of patients. Generally they are clinically insignificant. We picked this up on an imagining study; it doesn't have any clinical complications.

Intestinal diverticuli

What I mean by that is the colon. That last portion of your intestine is a tube. If you think about it, it is almost as if the tube developed an out-pouching. That out-pouching can get inflamed, can get infected, and can even rupture. That is a big problem, particularly for patients who have lost their kidney function, for reasons we really don't understand. But the sudden onset of abdominal pain in a patient who has ADPKD and has decreased kidney function, one of the things that should be considered is could this be a diverticula that has gotten into some trouble?

Hernias

There are two types of Hernias. Inguinal hernias are hernias down here in the crease between the lower part of your torso and your leg, Umbilical hernias are hernias that involve your belly button. Both probably develop due increased intra-abdominal pressure. You should keep an eye on these hernias. If a piece of bowel goes out through that hernia and the muscle then squeezes off, that can be a problem. But hernias are not something that every surgeon wants to run and do something about. In fact, if you have a surgeon who is talking with you on the way to the operating room, it is time to get a second opinion. You should pay attention to this. You want a consultation quiet in the office, not as you are being prepped for surgery.



Hepatic cysts in ADPKD: role of estrogens

Let me talk a little bit about hepatic cysts. It seems that there is a distinct hormonal component to the progression of hepatic cystic disease. This comes from a series of 85 women who were studied. The women who had never been pregnant and never taken hormone replacement therapy with estrogen had a very low incidence of hepatic cysts. The women who had never been pregnant but had taken estrogen replacement therapy, for example in a postmenopausal situation, had a significant incidence, 25 percent had cysts in their livers. The women who had been pregnant but had not had estrogen replacement therapy--it was a little higher, about 45 percent. The women who had done both, women who had had pregnancies as well as estrogen replacement therapy, again in a postmenopausal situation, had the highest rate of cysts in the liver.

I show this slide simply to say that estrogen seem to play a role in the development of liver cysts in ADPKD women because ADPKD women are the ones who by and large tend to have more symptomatic disease. This fact should be taken into consideration when we think about counseling women about pregnancies, about postmenopausal estrogen replacement, and although there are very limited data, from my perspective as a pediatrician and a pediatric nephrologist, when we counsel our young women patients about oral contraceptives.

Now one way potentially around this is to not have those estrogens see the liver. The way to do that is to apply them with a transdermal patch. As you probably know, there are forms of hormonal contraception that can be applied with a patch. That may be one therapy. Suffice it to say right now that we have limited information. We don't understand precisely how hormones can contribute to the progression of cystic disease, but it is a subject of intense study.



ADPKD - Special Issues

1. Pain syndromes - acute and chronic
2. Fertility
3. ADPKD in children

Fertility

Now some special issues. Fertility--I have actually had a number of young women express to me real concern about, "Doctor, can I get pregnant?" And the answer is yes. The answer for young men is yes, you can father children. In fact, there seems to be no problem at all with fertility in ADPKD. Young women often come to me worried about "I could have cysts on my ovaries." Well cysts in ovaries are actually quite common in the adult women population. A recent study from the University of Colorado PKD Program suggests that they are no more common in ADPKD women.

So then the next question arises, "But I could have polycystic ovary disease." Yes, you could. That is actually quite common. It occurs in about 10 percent of women, and it has nothing to do with ADPKD. Remember, ADPKD is a common disease. Polycystic ovary disease is a common disease. Two common diseases in certain situations can occur in a single individual. The basis for polycystic ovary disease has nothing to do with the mutation in ADPKD or the genetic defect in ADPKD. It probably has to do with insulin resistance in the body. In response to that, the ovaries make a lot of the male hormone called androgen. A lot of androgen running around the female body limits the ability to have regular periods, regular menses, limits the ability to get pregnant, can cause some of the male sex characteristics, like increased body hair, to be a problem. But this has nothing to do with ADPKD, per se.

I am going to spend a little bit more time on pain syndromes because, in fact, this is what brings the lion's share of people to medical attention. Then I am going to spend a few minutes on ADPKD in children.

00:00

ADPKD - Abdominal Pain

Cause

Frequency

Kidney

Cyst bleeding

++++

Stone	++
Infection	+
Liver	
Infection	rare
Cyst bleeding	very rare

Pain syndromes associated with ADPKD

There are two sets of pain syndromes. There is the acute onset of pain, and there is chronic pain. What I am going to talk about on this slide first is the acute onset of abdominal pain. That really has primarily two causes, unless again you have end-stage renal disease and you have to worry about colonic diverticula.

In the vast majority of people, it has two causes: one, something to do with what is going on in the kidney; the other, something to do with what is going on in the liver. In the kidney cyst bleeding is probably one of the most common causes of pain. As I will talk about in a little bit, many of the cysts in the kidney are walled off from the rest of the nephron. That means if you bleed into that cyst, there is nowhere for that blood to go, and that can cause pain. Cysts can rupture, and that can cause pain. Cysts can become infected, and that can cause pain. The acute onset of pain, particularly back pain, flank pain, or loin pain. You know, we read about this in the Bible, but I had to go and look up where loins are. Loins are actually here, the inside of your leg. There is a really good neurologic reason why pain from here tracks in that kind of arc-like way around to the front. So pay attention to that pain distribution. It can be unilateral, just on one side; or it can be bilateral, meaning both sides.

Stones, also. Particularly if the stone is making its way down the urinary tract and gets stuck. Urine builds up behind it. Things start to stretch. When hollow viscera.. when hollow organs in the body stretch unnaturally, it causes pain. A stone obstructing the urinary tract can cause pain.

In the liver pain is often associated with ...it is not so much a sharp pain as it is kind of a dull pain from just the burden of cysts in the liver or the size of some of those cysts in the liver. But every once in a while, you can get very severe right upper quadrant pain, and that could be because a cyst is infected, usually that is associated with a fever. You may even see a little bit of yellowish to your eyes because that is increasing the level of bilirubin in your blood. You're jaundiced. Or cysts can bleed. That seems, for reasons we don't understand, to be much less common in cystic liver disease than in cystic kidney disease.

Let me use this slide as a jumping off point to just say a brief word about chronic pain. This is not something that you think would ever happen in children, but I have had now a number of patients who have had chronic pain. It is really quite a miserable existence. It is miserable for the patient, it is miserable for the family, and it is miserable for the physician. The reason it is miserable for the physician, let me start there, is not because it is a pain in the neck, it is because your heart goes out to these people. They live day in and day out with either intermittent pain or worse, with unremitting pain. It colors the whole way they look at life.

And when it is a 12-year old child who doesn't want to get out of bed, who doesn't want to go to school, who doesn't want to eat, who doesn't want to play video games, who doesn't want to do anything, and doesn't even want to talk to you and you can't figure out what is going on, it is really quite atrocious. Chronic pain often is related to what is going on in terms of the cystic involvement in the kidney, at least as best we can understand. Patients who have massively enlarged kidneys and very big cysts often suffer from chronic pain. Sometimes those patients can be managed medically, particularly if it is an on- again/off-

again kind of thing. You can treat them with Tylenol, for example, and bed rest... plenty of fluids. The pain sometimes gets better.

In certain situations, particularly if it keeps coming back, a normal response of all of us to a chronically awful situation is depression. Actually for reasons that are very interesting from a pharmacological point of view, the tricyclic antidepressants can help with that depression, but they can also act in a helper way with other analgesics that you may be taking for chronic pain. In certain situations, that can be also addressed by relieving some of the cyst burden, putting a needle in and sucking the fluid out if you have a particularly big cyst. That has been helpful for several of my patients. Doing a laparoscopic exam and actually opening up the top of cysts so that they will drain can be helpful. And in certain situations, even surgery with cyst decompression can be helpful.

Then there is that small subset of patients who probably every one of you who has ADPKD in this room who participates in FRIENDS groups knows about. Those patients have chronic pain that just doesn't seem to respond to therapy. What those people need is they need to be understood. It is a horrible thing to live with pain day in and day out. They get depressed. They can't do what they need to do. They worry about the financial burden on their family. They worry about, if they are a parent, "What is going to happen to my child?" etc., etc. Here we really need a multidisciplinary approach to deal with their chronic pain. We need the advice of pain management specialists. We need the advice of psychologists and psychiatrists to help them cope with this. We need to think about medications that can be helpful. We need to think about approaches like biofeedback therapy, relaxation kinds of treatments, to help them with coping mechanisms to get through this. I think that is all very, very important. What they also need is understanding. They need to be accepted for "this is a miserable way to live, and we feel for you." It is just a really impossible situation. I can tell you this only having experienced it from the perspective of being a pediatric nephrologist, but I would imagine it is the same situation for adults.

00:00

	Early Onset	Childhood onset	Adult onset
Mean age of dx	prenatal-1 year	--	20-40 yrs
Unilateral disease	rare	up to 20%	rare
Hypertension	80%	15-30%	60%
Kidney stones	very rare	very rare	20-25%
ESRD	25%	rare	50%
extrarenal cysts	rare	rare	common
portal fibrosis	?	up to 15%	rare
ICA	rare	rare	10-15%
MVP	?	12%	25%

Two sorts of presentation of polycystic kidney disease in childhood

In terms of thinking about children, one thing that is very important to point out is that there are two sorts of presentations in childhood. One is a very special group of children who

present in the first year of life. By and large these children seem to have very severe disease, disease that is so severe that it really mimics in a lot of ways the recessive form of polycystic kidney disease. These children have a high incidence of hypertension, and many of them go on to develop renal insufficiency during their childhood.

But what is curious about ADPKD in children is that systemic manifestations really don't seem to be part of the picture for them except in older children with mitral valve prolapse. Older children can show up anywhere from toddlerhood all the way up to adolescence. Twenty-five percent of them or so present because they have symptoms. They either have an abdominal mass, they have flank pain--probably pain is the most common presenting symptom. The signs are flank mass, they are found to be hypertensive, they have a urinary tract infection, they are found to have blood or protein in their urine--those are the kinds of things that bring them to medical attention.

What is important for those of you who are parents, who have children with ADPKD, early on it can show up in one kidney. That doesn't mean... I mean we are all very logical people, "Well, if I take this out, the disease won't affect the other kidney". ADPKD is a bilateral disease, and sooner or later cysts will become clinically obvious in the other kidney. Why there is this asymmetry we don't understand. But I tell you this because I have gotten a number of phone calls from parents saying, "My child is going to have that cystic kidney out tomorrow. We know it is ADPKD because everybody in my family has ADPKD. Is that a smart thing to do?" And the answer is NO. It is not going to fix the problem, and you should be aware of that. Kidney stones are very, very rare, probably reportable in children. Children who show up later in childhood tend to hold on to their kidney function.

Why don't we stop here and take a 5- or 10-minute break, and then we will resume and finish the rest of this.

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