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Extrarenal Manifestations of Polycystic Kidney Disease

Part Three of Three



Dr. Robert Schrier

Dr. Robert Schrier, M.D.

Professor of Medicine, Chairman, Department
of Medicine, University of Colorado Health
Sciences Center, Denver, CO.

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00:00

**Frequency of extrarenal
manifestations of PKD**

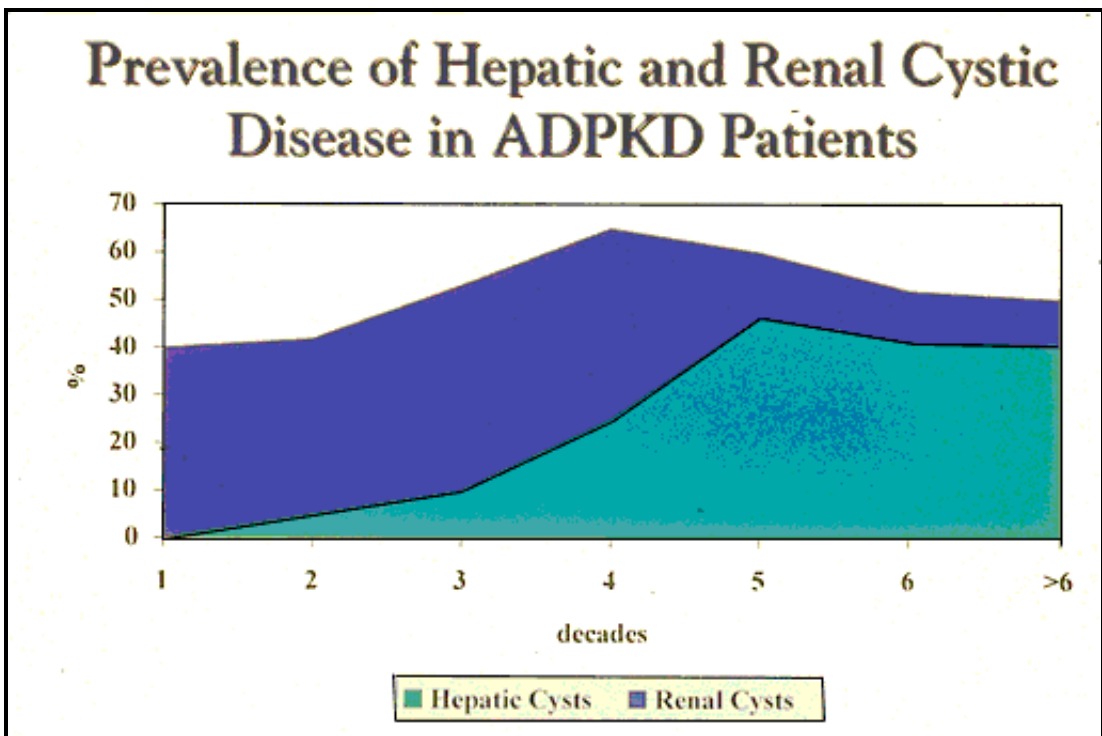
Manifestations of ADPKD

Manifestation	Freq (%)
Hypertension (?)	78
Hepatic cysts	75
Diverticulosis coli	70
Cardiac valve disorders	25
Intracranial aneurysms	10
Ovarian cysts	40
Inguinal hernias	15

Liver cysts in ADPKD

What about the liver cysts? This condition certainly doesn't have the morbidity and mortality that are associated with kidney disease and the cardiovascular disease, but liver cysts can be important in the morbidity of patients.

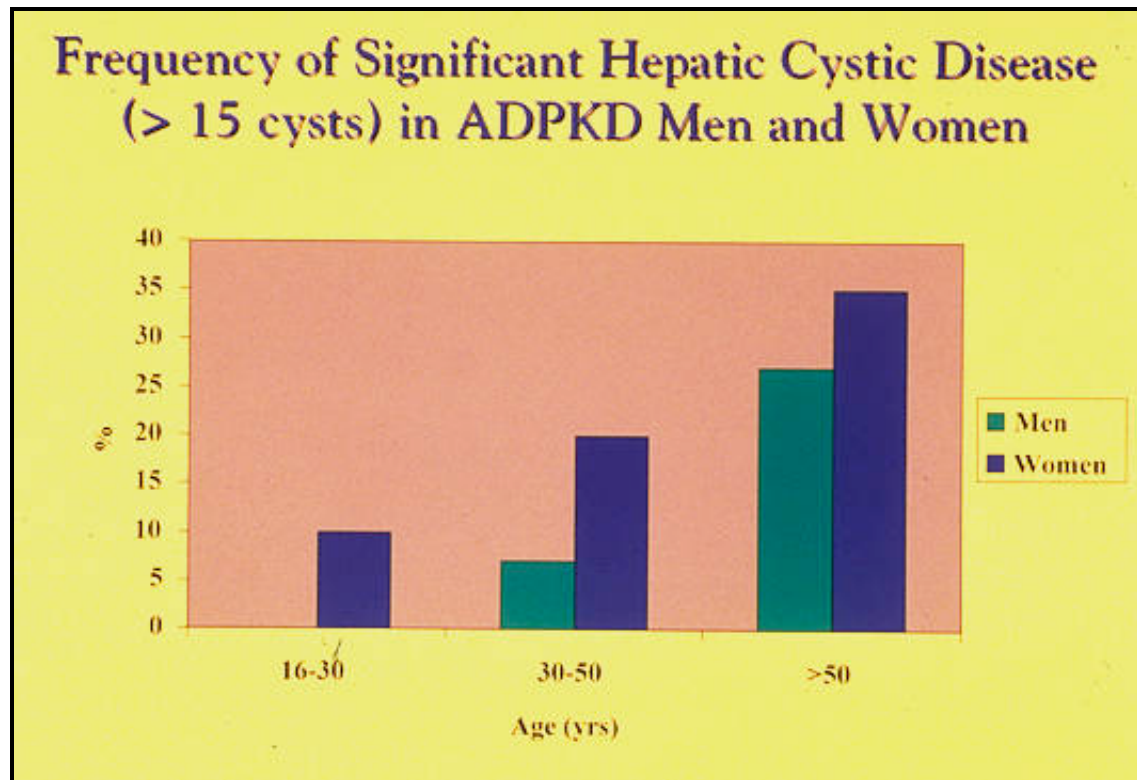
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Source: Gabow PA et al, Hepatology 1990 Jun;11(6):1033-7.

Liver cysts appear after kidney cysts in patients with ADPKD

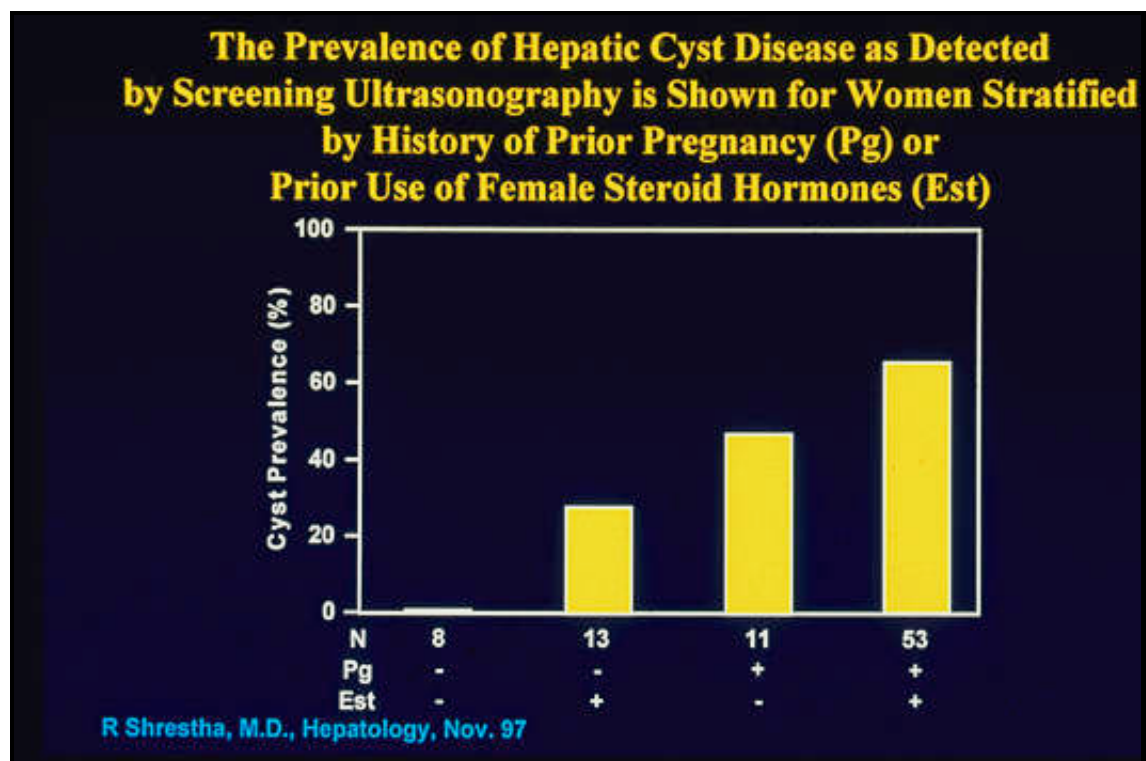
As you see, the renal cysts occur earlier than the hepatic cysts. We have another hypothesis which I would like to test. There is a substance called hepatic growth factor. Is the damage in the kidney occurring early, releasing hepatic growth factor, which we know is produced in the kidney, which then circulates to the liver and causes this proliferation of cysts? Is this why the liver cysts occur later than the kidney cysts? There are a lot of clinical questions that can be asked.



Source: Gabow PA et al, *Hepatology* 1990 Jun;11(6):1033-7.

Women have more liver cysts than men

One thing that we do know is that women have more liver cysts than men. If you examine this slide you can see this, the purple is the women with PKD at all ages.

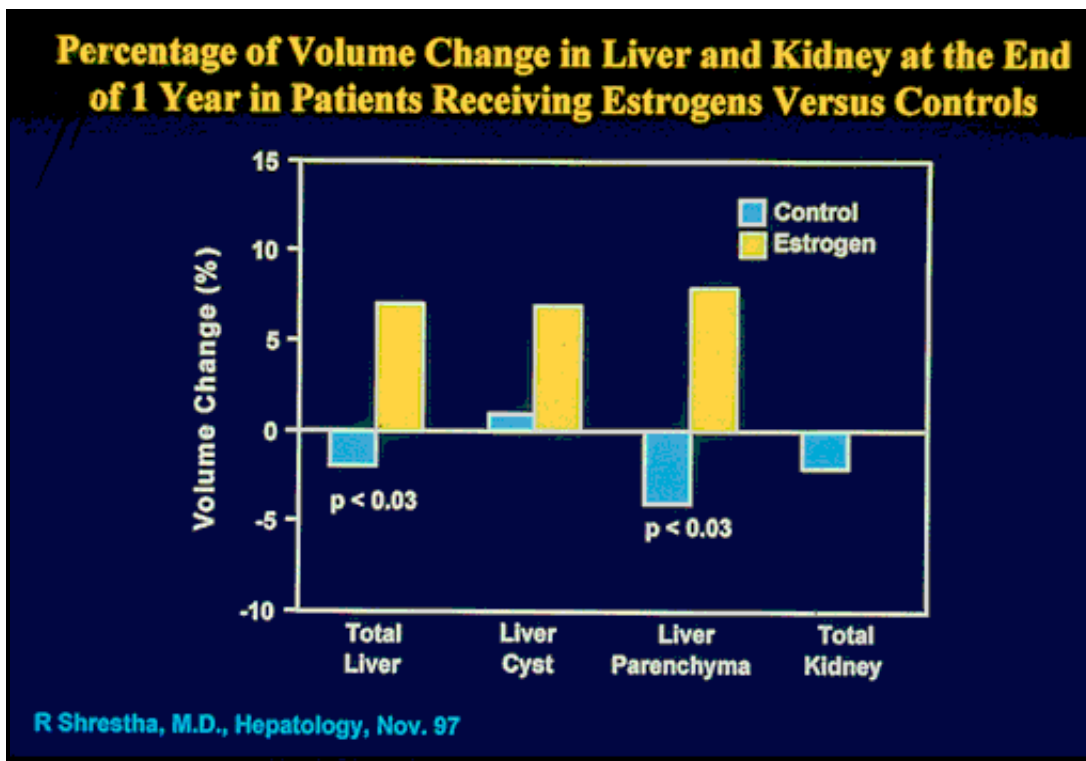


Source: Shrestha R et al, *Hepatology* 1997 Nov;26(5):1282-6.

Use of female hormones or prior pregnancy increase the risk for liver cysts

One can see that if you screen with ultrasound and look at the prior use of female hormones or pregnancy, these are the women who have both have the most cysts in the liver. So something about female hormones seems to stimulate these cysts in the liver but not in the kidney.

00:00



Source: Sherstha R et al, Hepatology 1997 Nov;26(5):1282-6.

Postmenopausal estrogen use increases risk of liver, but not kidney, cysts

This is an interesting study. These are postmenopausal women with polycystic kidney disease, some of whom took estrogen for one year and some of whom did not. Again, no effect on the kidney, but look at the effect of estrogen on the volume of liver cysts--total cysts, liver cysts, liver parenchyma. You can see that those women who took estrogens had an increase in liver cysts, an increase in liver size.

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Symptomatic polycystic liver disease in patients with ADPKD

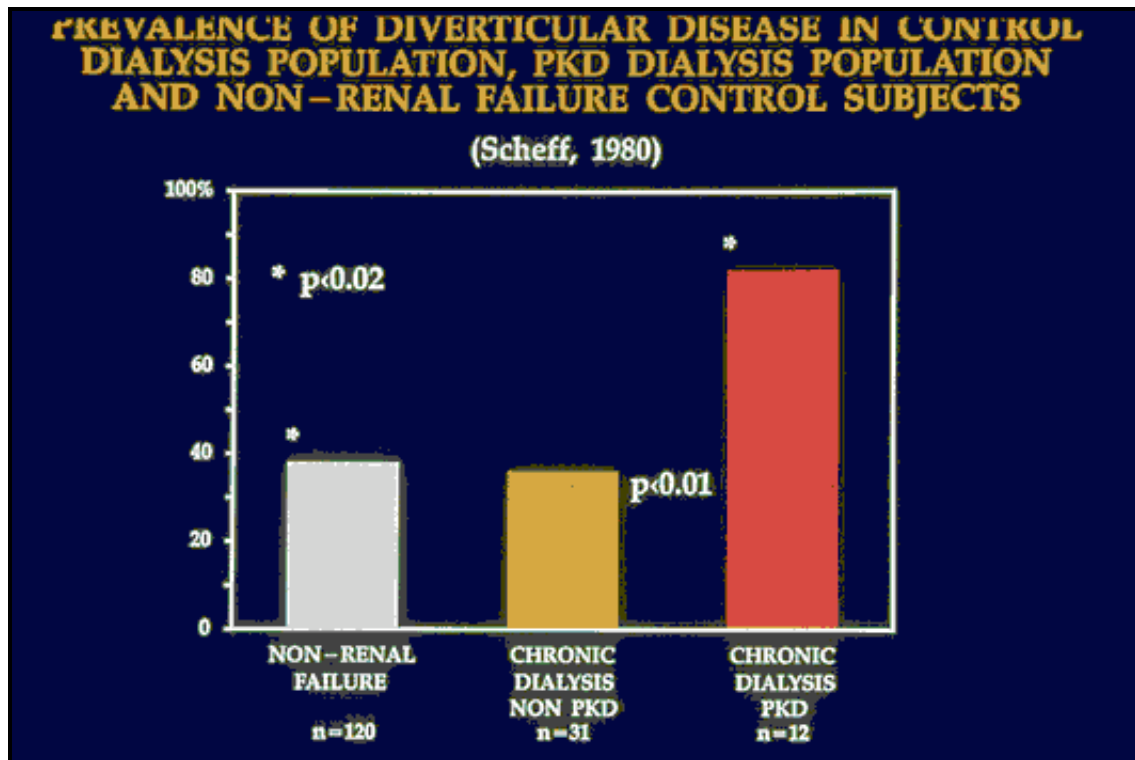
- **Complicated cyst**
 - Hemorrhage
 - Rupture
 - Infection
- **Mass effect**
 - Distension, discomfort, dyspnea, heartburn, early satiety, malnutrition
 - Inferior vena cava (IVC) /hepatic veins: Hepatic vein occlusion with ascites

- IVC below hepatic veins: edema, thrombosis
- Biliary extrinsic compression: cholestasis, filling defects on ERCP. MR cholangiopancreatography

Complications of liver cysts in ADPKD

Do liver cysts make any clinical difference? It can make a difference though the effect, magnitude-wise, is certainly much less than most areas that we have talked about. But you can hemorrhage into those liver cysts, they can rupture, they can become infected, they can block the vena cava... in fact it can do a lot of things. I am sure Dr. Torres is going to speak about this sometime in this conference.

00:00



Source: Scheff RT et al, Ann Intern Med 1980 Feb;92(2 Pt 1):202-4.

Diverticulosis in ADPKD

Remember we talked about the outpouchings, the diverticula, in the intestines? Well, some of the patients who have gone on dialysis will rupture these, get an infection in their abdomen and do very poorly. So it is shown here.

Here are chronic dialysis patients without PKD versus PKD. You can see much more diverticulosis in the patients with polycystic kidney disease. When you are on dialysis, your immune system is suppressed. You can't fight infection as well. So rupturing a diverticulum is very dangerous in any person but particularly a patient on dialysis.

00:00

Nephrolithiasis in ADPKD Patients

- ◆ The frequency of renal stone disease in

ADPKD patients ranges from 8 - 36% as compared to a cumulative incidence of 12 and 5% in men and women respectively in the general population.

- ◆ The diagnosis of renal stones in ADPKD is often hindered by distorted anatomy and cyst rim calcifications

Kidney stones in patients with ADPKD

Back to the kidney stones--their prevalence in PKD patients ranges from 8 to 36 percent, 12 and 5 percent in men and women, respectively. It is not so easy, because of distorted anatomy, to make the diagnosis of renal stones in PKD patients.

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Metabolic Abnormalities in PKD and non-PKD Patients with Nephrolithiasis

Metabolic Abnormality	With ADPKD (%)	Without ADPKD (%)
Hypocitraturia	67	19
Hyperoxaluria	19	16
Hyperuricosuria	15	38
Hypercalciuria	11	39
Parathyroidism	5	5

Source: Torres VE et al, Am J Kidney Dis 1988 Apr;11(4):318-25.

Importance of low citrate excretion (hypocitraturia)

Here is what I was talking about as far as citrate. Hypocitraturia, which predisposes to kidney stones, is present in 67 percent of PKD versus 19 percent in non-PKD patients. So back to the triple therapy that I mentioned--it is available. Thirty percent of patients whose blood pressure is being controlled are taking ACE inhibitors. We just finished a study in diabetes getting blood pressure down to 125/75 without complications. The nice thing about the patient with polycystic kidney disease is, that unlike diabetes where every organ is affected, PKD patients are generally healthier. Potassium citrate is used for hypocitraturia

and kidney stones. This is not experimental medicine.

00:00

Classification of Renal Stones in Patients with and without ADPKD

COMPOSITION	ADPKD %	CONTROL %
Uric Acid	57	10
Calcium oxalate	47	70
Calcium phosphate	20	20
Struvite	10	9

Source: Torres VE et al, Am J Kidney Dis 1988 Apr;11(4):318-25.

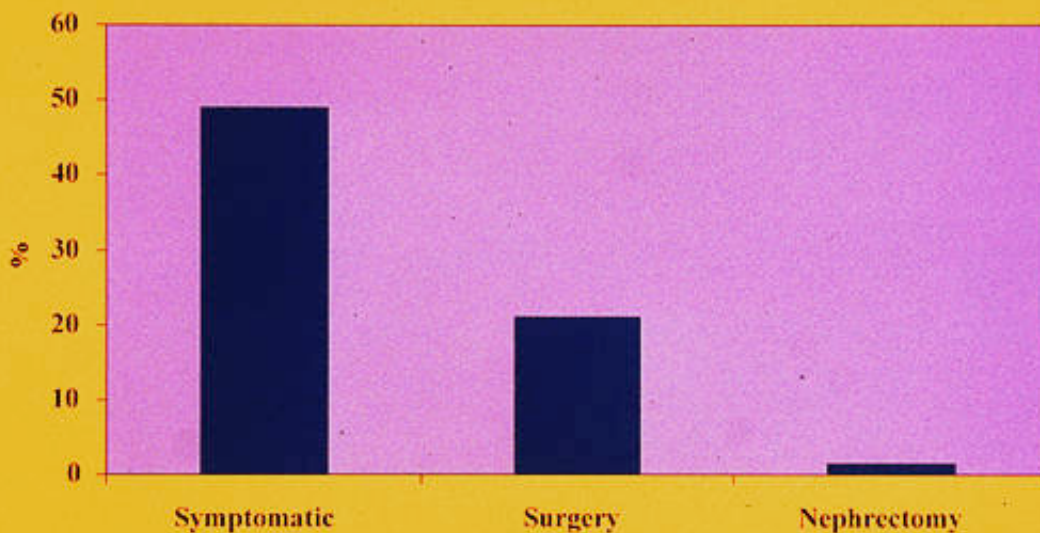
Source: Torres VE et al, Am J Kidney Dis 1993 Oct;22(4):513-9.

Types of kidney stones found in patients with ADPKD

These are the types of kidney stones that the patients with PKD get. You can see uric acid and so forth.

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Morbidity of nephrolithiasis in 151 Mayo Clinic ADPKD patients

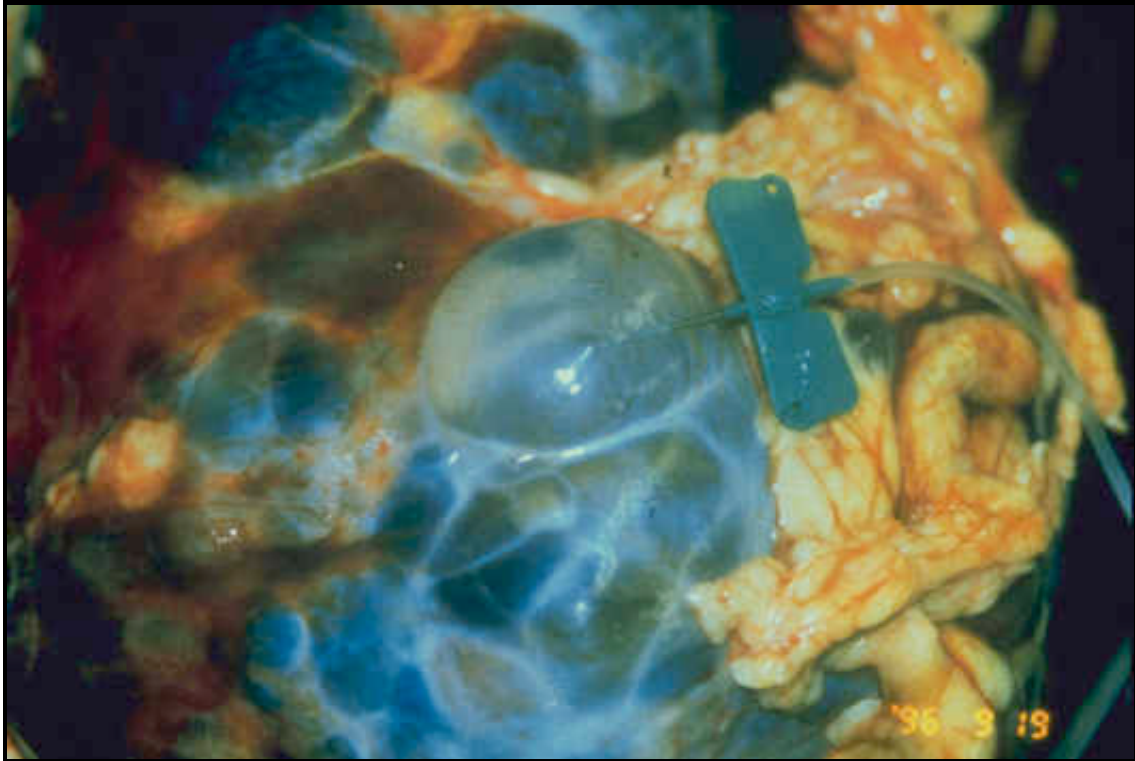


Source: Torres VE et al, Am J Kidney Dis 1993 Oct;22(4):513-9.

Morbidity from nephrolithiasis in ADPKD patients

These data are from the Mayo Clinic. In PKD patients with kidney stones, 50 percent were symptomatic, 20 percent needed surgery, and a very small percent actually lost their kidney. If you have bilateral kidney disease due to polycystic kidney disease, you don't want to lose a kidney. And you certainly don't want your kidneys to get infected.

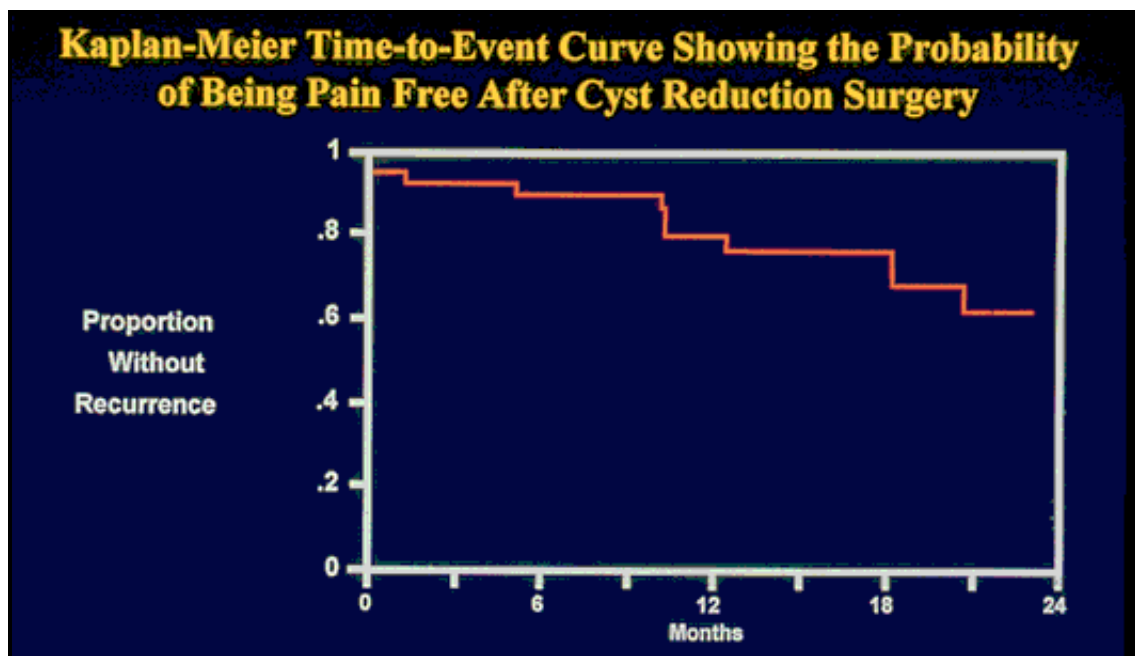
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Kidney cysts can be quite large, causing pain

These big cysts in polycystic kidney disease can cause a lot of pain.

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Source: Brown JA et al, J Urol 1996 Jul;156(1):22-7.

Benefits of cyst reduction surgery in terms of pain

We know now that if one decreases the large cyst size, injects alcohol so they don't re-expand or deroofs them, as has been done in Oregon and the Mayo Clinic, a decrease in abdominal pain is found. But eventually, the time of being pain-free gradually decreases.

00:00

Aneurysmal Subarachnoid Hemorrhage (SAH) in ADPKD

- ◆ Incidence 1:2089 person yr (5x rate in gen. Pop.)
- ◆ Rupture at a younger age (40-45 yr) often when renal function still normal (> 50%)
- ◆ 25 - 50% of intracranial hemorrhages in ADPKD
- ◆ Mortality: 35% of those who make it to a hospital
- ◆ Cause of death in ~5% of ADPKD patients
- ◆ 2% of all aneurysmal SAH are associated to ADPKD

Intracranial aneurysms in patients with ADPKD

What about aneurysms? They occur in PKD patients at about five times the rate in the general population and unfortunately occur at a young age and can lead to an intracranial hemorrhage when the kidney function is normal, and can be fatal in 35 percent of these patients. It causes death in approximately 5 percent of PKD patients, and 2 percent of all aneurysms in all patients that lead to subarachnoid hemorrhages are associated with PKD. That means 98 percent of subarachnoid hemorrhages occur in patients without PKD.

On the other hand, do you look for big kidneys if someone has a ruptured cerebral aneurysm very early in life to make sure they don't have polycystic kidney disease? The answer to that question is yes.

00:00

Intracranial Aneurysms in ADPKD

STUDY	TORRES	CHAPMAN	HUSTON	RUGGIERI
Year	1990	1992	1993	1994
Method	CT/MRI	CT/ANGIO	MRA	MRA
N	96	88	85	93
Pts with aneurysms	0	4	9	10
Suspicious	11	4	-	-

Source: Torres VE et al, *J Am Soc Nephrol* 1990 Jul;1(1):84-90.
Source: Chapman AB et al, *N Engl J Med* 1992 Sep 24;327(13):916-20.
Source: Huston J 3d et al, *J Am Soc Nephrol* 1993 Jun;3(12):1871-7.
Source: Ruggieri PM et al, *Radiology* 1994 Apr;191(1):33-9.

Incidence of intracranial aneurysms in ADPKD

These are different studies. It used to be thought that the incidence of intracranial aneurysms was much higher. Now there are studies from a number of institutions using sensitive techniques, and the incidence is much lower than had previously been suggested.

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Characteristics of ADPKD Patients with Ruptured Intracranial Aneurysms			
	Denver CO N = 22	Rochester MN N = 33	Paris, France N = 71
Age (yrs)	38	47	39
Male:Female	8:14	17:16	32:39
Family history (%)	20	22	18
Multiple (%)	40	24	31
Morbidity/Mortality (%)	89	61	46
Recurrent	4/6	NA	8/71

Characteristics of ADPKD patients with aneurysms

The characteristics of patients: Family history. If someone has a family history of ruptured aneurysm in a relative with PKD, it is probably worth screening the patient for intracranial aneurysm. There are very sensitive methods now for screening such as MRI angiography. Certainly if the patient had a previous ruptured aneurysm and then starts having some

Management of Unruptured Intracranial Aneurysm in ADPKD

Surgery

- ◆ Unruptured, but symptomatic
- ◆ Concurrent at surgery for ruptured aneurysms, If technically possible
- ◆ Incidental, ≥ 10 mm

Reassurance and Re-evaluation

- ◆ Incidental, ≤ 5 mm

Controversial, dependent on patient's attitude and individualities

- ◆ Incidental, 6-9 mm

Management of unruptured intracranial aneurysms in ADPKD

This slide summarizes the management of unruptured intracranial aneurysms. The main point is, that if it is greater than 10 mm, it probably ought to be clamped off. If, during surgical clamping of a ruptured aneurysm, an unruptured one is seen, it is reasonable to clamp the second aneurysm, also. If an aneurysm on screening is less than 5 mm, then it is best to re-evaluate at a later date. The approach to aneurysms 6 - 9 mm in diameter is a grey zone and you have to discuss with the patient options of surgery vs. observation.

Arachnoid Cyst in ADPKD

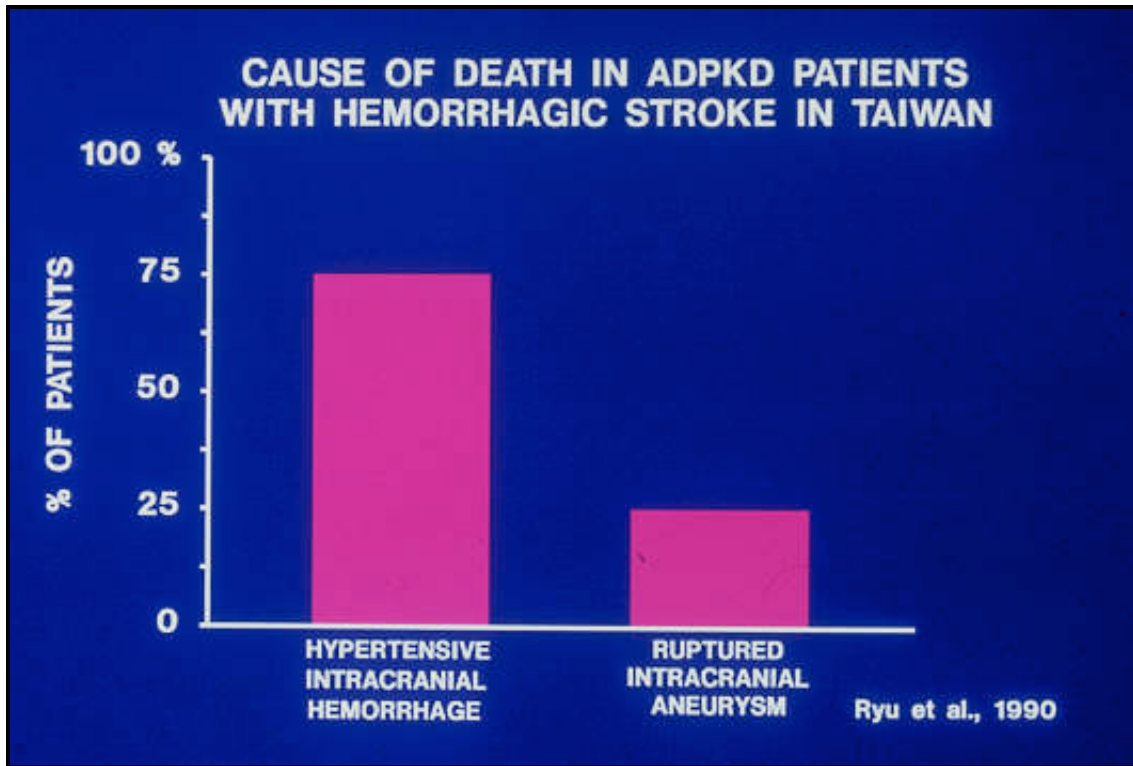
Arachnoid Cyst

- ◆ 8% of ADPKD patients
- ◆ Asymptomatic, but five-fold increased risk of subdural hematoma
- ◆ No treatment indicated

Arachnoid cysts in ADPKD

Arachnoid cysts occur in 8 percent of patients. No treatment indicated, but they do have a five-fold increased risk of a subdural hematoma.

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Source: Ryu SJ et al, Stroke 1990 Feb;21(2):291-4.

Risk of intracranial bleeding from hypertension vs. from an aneurysm

This is the last slide, and it comes back to high blood pressure. Even though people worry about ruptured cerebral aneurysms in polycystic kidney disease, if you look at the percent of PKD patients and the cause of death due to hemorrhagic stroke--these data are from Taiwan-- intracranial hemorrhage related to high blood pressure is many fold greater than a ruptured cerebral aneurysm. So control high blood pressure! Control high blood pressure! Control high blood pressure!

Thank you very much for your attention.

Discussion

Moderator:

One question relates to what we call white-coat syndrome. How do you know that the blood pressure that you measure in the office is truly reflective of what your blood pressure is at all times, knowing that there can be a variation in your blood pressure at home versus that in the office?

Dr. Schrier:

That is a good question. I think anyone who has polycystic kidney disease at any age ought to have a sphygmomanometer (blood pressure cuff) and measure their blood pressure at

home because there can be differences between office blood pressure and blood pressure at home. Also there can be differences between daytime and nighttime blood pressure.

We know that in normal individuals blood pressure dips at night by 10 mm Hg or about 10 percent. Some patients with renal failure, and patients who are elderly, obese, and diabetic don't decrease their blood pressure at night. So their blood vessels are exposed to high pressures for 24 hours a day because they are not decreasing at night. I think any patient with polycystic kidney disease ought to have a sphygmomanometer at home and ought to be taking their blood pressure and reporting their blood pressure and sharing that with their doctor.

Audience member:

Does weight loss help in controlling blood pressure if one is overweight?

Dr. Schrier:

Weight loss is important and I am glad you asked that. It turns out that even if you only lose about 10 percent of body weight, and you don't have to get down to normal weight, blood pressure decreases. Someone who is way overweight but loses a relatively small amount and keeps it down, that brings their blood pressure down. We also know that exercise, independent of weight loss, also will decrease blood pressure.

And then there is the question of salt intake. Salt intake is sometimes controversial as far as how much you have to restrict it. But if you use fresh vegetables, fresh fruit--you don't use canned goods and you don't salt your food-- then you really have adequate sodium restriction. This salt restriction also can have a reasonable effect on high blood pressure. Exercise, lose weight, restrict sodium.

Audience member:

How should hypertension be treated in someone who has had high blood pressure for many years and who only recently has found out that he has ADPKD?

Dr. Schrier:

The question is a gentleman has had high blood pressure for a long period of time but only three months ago was found to have polycystic kidney disease. We know blood pressure goes up with age, at least in Western societies, but we also know that PKD causes high blood pressure by itself.

Clearly you can't change your age. We don't know the answer to what type of medication to use. I presented what I hope is a relatively compelling story for using as the first drug an angiotensin converting enzyme inhibitor. But in large studies that are randomized and prospective, this has yet to be proven. It has been proven that ACE inhibition is effective in controlling blood pressure and reversing left ventricular hypertrophy in PKD patients.

I think it is hard to argue with the seven-year study where blood pressures came down. But about 50 percent of those patients had to add a second or third drug. So you might start out with an angiotensin converting enzyme inhibitor.

There is one caveat: Arlene and I reported in the *Annals of Internal Medicine*, ([Chapman AB et al, Ann Intern Med 1991 Nov 15;115\(10\):769-73.](#)) that in some PKD patients who had big kidneys already and had substantial kidney function loss, the angiotensin system constricts the outgoing blood vessel from the glomerulus. So you open up the outgoing glomerular blood vessel by blocking the angiotensin system, and kidney function can decrease.

For this reason, within a week of starting a PKD patient on an ACE inhibitor, one should measure serum potassium and serum creatinine. The drop in kidney function after addition of an ACE inhibitor generally occurs in the patient who is already receiving a diuretic.

However, even if kidney function falls after starting an ACE inhibitor, it often will fall only modestly and stabilize. That may be good because it may be the blood pressure within the glomerulus that is important as far as how fast the kidney function deteriorates.

Some physicians believe the following: Elderly patients, and patients with kidney disease are salt sensitive. If they take a lot of salt, their blood pressure goes up. I would like to start with a diuretic. If that doesn't work, I would like to add a calcium channel blocker. If that doesn't work, I would like to add a third one, an alpha blocker. I can't argue with them now. We don't have the data. The renin-angiotensin system is contributing to the high blood pressure. But does it mean that ACE inhibition is the preferred first treatment? We need to study this issue.

As I showed you in the study that we hope will be funded, I would try to get the blood pressure down to 125/75 and I would give potassium citrate.

Audience member:

Are angiotensin receptor blockers also useful in ADPKD?

Dr. Schrier:

It has been shown that angiotensin converting enzyme inhibitors do not totally block angiotensin formation, and there may be some other pathways for angiotensin production other than this converting enzyme, so why don't we use something that blocks the angiotensin receptor? To contract blood vessels, angiotensin has to attach to a receptor on the vascular smooth muscle cell.

Within the next year there are probably going to be six or eight angiotensin receptor blockers available. Whether or not they are going to be better than the ACE inhibitors I don't think we know. The one clear advantage now is, that in 5- 10 percent of patients (and it can go up to 10 - 20 percent in people who have heart failure) there is cough associated with taking an ACE inhibitor. This problem with cough doesn't occur with an angiotensin receptor blocker.

On the other hand, the ACE inhibitor not only brings angiotensin down but stimulates another hormone called bradykinin. Bradykinin is a potent stimulator of nitric oxide. Nitric oxide is the most potent vasodilator known. There is evidence now that the ACE inhibitors work to lower blood pressure not only by decreasing angiotensin but also by increasing bradykinin-mediated nitric oxide.

So I don't think, except for cough, we can clearly say that angiotensin receptor blockers are going to be better. We know that they are going to be more expensive because they are still on patent. But theoretically the ACE inhibitors could be better. This is another clinical study that needs to be done: comparing ACE inhibitor drugs versus angiotensin receptor blockers in PKD patients.

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