Higher BMI May Explain Womens' Lower Risk of End Stage Renal Disease Compared with Men

Lifestyle factors, particularly higher body mass index (BMI), appear to explain the lower risk of end stage renal disease (ERSD) in women compared with men, according to data from the Chronic Renal Insufficiency Cohort (CRIC) Study presented at Kidney Week 2016.

The incidence of ERSD is 1.5 times higher in US men than women even though women live longer and are more likely to have chronic kidney disease (CKD), said Ana C. Ricardo, MD, MPH, MS, assistant professor of medicine at the University of Illinois at Chicago. Some studies have shown that men with CKD progress more quickly (Neugarten J, et al. *Am Soc Nephrol* 2000; 11:319–29).

The effect of gender on CKD progression has been hotly debated for years. Until about 15 years ago there was a consensus that gender had no effect, then the prevailing view shifted to see female gender as protective, said Joel Neugarten, MD, JD, professor of medicine at Albert Einstein College of Medicine. A large meta-analysis published 2 years ago reignited the debate when it found no gender-based difference in CKD progression (Nitsh D, et al. *BMJ* 2013; 346:f324), a result Neugarten attributed to the high number of patients with diabetic renal disease in the study.

Now, Ricardo and her colleagues are wading in to the debate with an analysis of the relationship between gender and progression to ERSD (determined based on dialysis or transplant and estimated glomular filtration rate) in the Chronic Renal Insufficiency Cohort (CRIC). The CRIC study followed 1778 women and 2161 men for an average of about 7 years. The average age of study participants was 58; 42% were non-Hispanic black and 13% were Hispanic.

They found that at the start of the study women were more likely than men to be physically inactive (33% vs. 28%), never have smoked (53% vs. 39%), and have a higher BMI (33 vs. 31 kg/m^2). During the study follow-up period, 844 participants developed ERSD, and women's risk was lower, but nearly disappeared when the researchers adjusted for lifestyle factors, including smoking, physical activity, and BMI.

"In the unadjusted analysis, in men kidney function tended to get worse over time at a more rapid rate than women," Ricardo said. But after the researchers adjusted for baseline kidney function and markers of bone and mineral metabolism, the gender differences in progression became less significant. Adjusting for lifestyle factors also reduced the differences.

Adjusting for BMI alone appeared to attenuate the risk of ERSD on its own in women. This "obesity paradox" has also been documented in previous studies, Ricardo noted.

"We know that in the general population obesity is a risk factor for cardiovascular disease and death; however, in dialysis patients having higher weight or BMI is protective," she explained.

Higher rates of smoking among men did not appear to explain the differences.

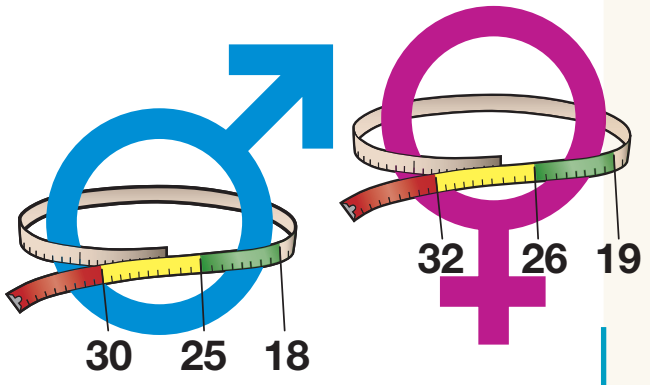
"In other studies, we've seen that smoking has a deleterious effect [on the kidney]," Ricardo said. "But for this particular study it didn't appear to play a significant role in terms of [gender] disparities."

The risk of mortality in women was 40% lower than in men, Ricardo said, so more women were not dying before reaching dialysis or transplant.

"It's a well-studied, well-followed cohort that confirms a relationship between gender and renal disease," said Neugarten.

But it also raises questions about the role of sex hormones in CKD progression. For example, if estrogen were protecting women from faster progression of renal disease you would expect younger women to be protected and older women to progress more quickly. "But younger women had accelerated progression compared to older women," Neugarten said. "That's contrary to what I would have predicted."

The findings on BMI were also surprising. There



isn't a clear mechanism to explain this relationship, Neugarten noted. Also, BMI as a measure is considered by many to be flawed, he said. But other studies that have used waist circumference or other measures of obesity have found contradictory results as well.

"The consensus is that high BMI accelerates renal disease, but many investigations have found that it is protective," he explained. "We don't know."

In future analyses, Ricardo and her colleagues plan to look at whether estrogen helps protect women from ERSD. They also plan to look at whether gender differences in endothelial function between men and women play a role.

In the meantime, she noted that many of the factors that appear to put men at greater risk based on her analysis are modifiable. For example, interventions might include management of phosphorus, calcium, or addressing issues related to socioeconomic status.

"We could potentially bring the risk of men down," Ricardo said.

She said her analysis also identified important disparities in the care women receive. Women were less likely to receive cardioprotective medications, like ACE inhibitors, angiotensin inhibitors, statins, or aspirin. They were also less likely to be seen by a nephrologist.

We nephrologists need to see if we are treating women the same way as men," she said.

Organoids Derived from Patients with Kidney Disease May Aid Research

Chicago—Stem cells from patients with polycystic kidney disease have been coaxed into growing into kidney-like structures, which may aid researchers studying the disease, according to a study presented at Kidney Week 2016.

Ryuji Morizane, MD, PhD, an instructor and scientist in the Brigham and Women's Hospital Renal Division in Boston, and his colleagues presented data on how they grew the kidney-like structures, called kidney organoids. They also described the features of the kidney organoids and the disease features they recreate.

Improvements in cell culturing technology have allowed scientists to coax stem cells into growing into organoids that recapitulate many of the features of kidneys, lungs, the gut, brain, and retina (Clevers H. *Cell* 2016; 165:1586–97). Scientists can use organoids to study organ development and disease processes in the laboratory, noted Hans Clevers, MD, PhD, professor of molecular genetics at the Hubrecht Institute in Utrecht, Netherlands, in his review. Organoids derived from the cells of patients with diseases, in particular, hold the promise to aid personalized medicine, he noted.

Morizane and his colleagues had previously developed a method to grow kidney organoids from human pluripotent stem cells that have the basic features of the kidney, including segmented nephron structures containing podocytes, proximal tubules, loops of Henle, and distal tubules juxtaposed to interstitial cells. Now, they have applied this method to pluripotent stem cells collected from patients with autosomal recessive polycystic kidney disease (ARPKD). The patients' cells grew into kidney organoids that had large cysts in the tubules, just like those seen in patients with ARPKD.

"Establishment of a novel platform to model ARPKD using human kidney organoids will facilitate studies on mechanisms of cyst formation and contribute to the development of chemical screening systems to find potential therapeutic agents for polycystic kidney disease," said Morizane.

The work may also lay the groundwork for one day growing transplantable kidneys in the laboratory.

"Our organoid system enables *in vitro* studies of kidney pathophysiology, nephrotoxicity assays, and disease modeling, and ultimately will lead to development of bioengineered kidneys for regenerative medicine," Morizane said.

Clevers said Morizane's study builds on work by another laboratory that has generated kidney organoids from human stem cells (Takasato M, et al. *Nat Proc* 2016; 11:1681–1692). It also demonstrates the potential of stem cells to form remarkably organ-like structures.

"This beautiful study builds on earlier work by Melissa Little and her colleagues in Melbourne," Clevers said. "It is amazing to witness again the self-organizing capacity of stem cells. The only thing missing from these mini-kidneys is the plumbing: blood vessels and ureter."

"Kidney organoids derived from human pluripotent stem cells contain multiple kidney compartments and model polycystic kidney disease" (Abstract 2139).