Studies Shed Light on Link Between APOL1 Gene Variants and Kidney Disease in African Americans

By Tracy Hampton

Links between variants in the APOL1 gene and kidney disease in African Americans are among the strongest genetic associations reported for a common disease, according to recent findings. The research could help identify patients who need early treatment and help researchers identify how variants in the gene wreak havoc on the kidneys.

The findings were reported in several recent articles published together in the Journal of the American Society of Nephrology (JASN).

“The five articles published in JASN launch a new era in investigating the underlying risks for developing two very common and complex kidney diseases in African Americans,” said Eric G. Neilson MD, editor-in-chief of JASN. “Susceptibility variants such as those in the APOL1 gene give scientists new tools for diagnosing and understanding certain diseases, and they could eventually provide new targets for drug therapy.”

APOL1, sleeping sickness, and kidney disease

Compared to European Americans, African Americans are four to five times more likely to develop kidney failure, and family members of African Americans with kidney failure have an even greater risk of developing it. This suggests that genetics may be at play.

Previous studies have found that variations in the APOL1 gene cause up to 40 percent of kidney disease in African Americans who undergo dialysis or kidney transplantation and that APOL1 kidney risk alleles are present only on the chromosomes of individuals of re-

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Bedtime Dosing of Antihypertensives Can Reduce Cardiovascular Risks for CKD Patients

Taking at least one hypertensive medication at bedtime instead of upon waking can reduce the risk of cardiovascular events by as much as two thirds, reports Ramón C. Hermida and associates in the December Journal of the American Society of Nephrology (JASN). This simple and costless approach could lead to significant improvements in outcomes for patients with high blood pressure (BP) whether or not they have chronic kidney disease (CKD) and could change how nephrologists administer antihypertensive drugs for their patients.

Circadian rhythms and blood pressure dipping

There is a natural tendency for BP to drop during sleep. But people with high BP have a tendency to not experience this dip and may even have a rise in BP at night. These patients—non-dippers and reverse dippers—tend to be at a higher risk for experiencing cardiovascular events.

Chronotherapy—using the body’s

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Bedtime Dosing of Antihypertensives

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circadian rhythm patterns to increase the efficacy of medications—is being studied in a wide variety of diseases, including cancer, asthma, and arthritis. The cardioprotective effects of using chronotherapy to administer hypertensive medications at bedtime have been previously studied (Smolensky MH, et al. Blood Press Monit 2010; 15:173–180), but this was the first study to confirm the effect by using ambulatory blood pressure (ABMBP) monitoring data.

“A large number of published prospective trials have reported clinically meaningful morning-evening, treatment-time differences in BP-lowering efficacy, duration of action, safety profile, and/or effects on the circadian BP pattern for different classes of hypertension medications,” Hermida said.

The group previously reported that urinary albumin excretion was significantly reduced with the nighttime dosing of valsartan (Hermida RC, et al. Hypertension 2005; 46:960–968). Hermida called the finding “just one single example of too many similar findings for many hypertension medications.”

The MAPEC (Ambulatory Blood Pressure Monitoring and Cardiovascular Events) study, from which the current report in JASN was derived, “was designed to test exactly what we documented, and the results were expected,” Hermida said. “We were, however, surprised by the extent of the differences between groups.” The MAPEC study appeared in Chronobiology International in 2010.

“There has been a longstanding concern about the lack of good nocturnal BP control in many patients with hypertension, including those with CKD,” said Frank C. Brosius III, MD, chief in hypertension and kidney disease. “However, albeit some evidence that nocturnal hypertension persisted in many patients, I am not aware of previous randomized controlled trials that have examined the impact of bedtime therapy on nocturnal BP control in CKD patients.”

Ambulatory blood pressure monitoring

Between 2000 and 2007, Hermida and his colleagues at the University of Vigo in Spain conducted a prospective open-label investigation with 661 patients randomly assigned to either take at least one antihypertensive medication at bedtime or take all their medications upon waking in the morning. At the beginning of the study period, both groups had similar renal and cardiovascular profiles.

Patients were monitored for two endpoints: 1) total cardiovascular events, including death, myocardial infarction (MI), angina pectoris, revascularization, heart failure, artery occlusion, and stroke, and 2) major cardiovascular events (cardiovascular death, MI, and stroke). This focus is important because “there have been relatively large studies of the effect of such therapy on ‘hard’ cardiovascular end-points in CKD patients,” Brosius said.

The investigators were able to capture the real-time data needed to confirm the beneficial effects of bedtime dosing through the use of ABMBP monitoring. Each patient wore a portable BP monitor for 48 hours before each follow-up visit, and BP measurements were recorded every 20 minutes during the day and every 30 minutes during the night. Asleep and awake periods were verified with actigraphy to ensure accurate data capture. Although previous research has confirmed the importance of nighttime BP in predicting the risk of cardiovascular events, this was based only on the AMBP data obtained at the beginning of the study, with no ABMBP data captured in the follow-up period.
Significant cardiovascular outcomes

After a median follow-up time of 5.4 years, patients in the bedtime dosing arm had experienced 35 cardiovascular events compared with 104 events in the morning dosing arm. Major cardiovascular events affected 9 of the patients in the bedtime dosing arm, compared with 26 events in the morning dosing arm. In addition to the primary endpoints of cardiovascular outcomes, patients taking at least one medication at bedtime also experienced better outcomes in reducing albumin excretion.

“These treatment-time–dependent effects on sleep-time BP control were strongly associated with lower risk of [cardiovascular disease] events,” the group determined. “Indeed, the progressive reduction in the asleep BP mean from baseline was the most significant predictor of event-free survival.

“The results indicate that [cardiovascular disease] event rates in patients with hypertension can be reduced by more than 50 percent with a zero-cost strategy of administering blood pressure-lowering medications at bedtime rather than in the morning,” Hermida said, adding that “differences between treatment-time groups were greater than anticipated due to some extent to the very minor number of events in the group of patients who were ingesting not just one but all medications at bedtime.”

Brosius found the results “striking and provocative, but cautioned that "since this is a single-center study and because of the degree of risk reduction, these results need to be confirmed in a larger, multiinstitutional randomized controlled trial.”

Hermida concurred: “The current report in *JASN* is just a subgroup analysis from the much larger MAPEC study. Fully comparable results, also derived from our much larger study, have been previously reported for subgroups of patients with diabetes (Hermida RC, et al. *Diabetes Care* 2011; 34:1270–1276), resistant hypertension (Hermida RC, et al. *Chronobiol Int* 2010; 27:1629–1651), or for the general hypertension population (Hermida RC, et al. *J Am Coll Cardiol* 2011; 58:1165–1173). These findings, however, will need further corroboration by larger studies.”

Hermida and his colleagues are currently coordinating a multicenter prospective trial with the participation of primary care centers from Northwest Spain to corroborate the findings. Termed the Hygia Project, the new trial will test hypotheses similar to those from the MAPEC study. So far the team has recruited over 9000 patients who are being followed by repeated 48-hour ABPM monitoring.

And despite the single-center scale of the current study in *JASN*, Brosius said that “since there is no known adverse consequence from nocturnal dosing of most antihypertensives I, for one, will consider more regularly prescribing these medications at bedtime, as well as in the morning.”

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