UT SOUTHWESTERN MEDICAL CENTER NEWS

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Anti-aging hormone *Klotho* may prevent complications in chronic kidney disease, UT Southwestern research suggests

DALLAS – Feb. 17, 2011 – Low levels of the anti-aging hormone Klotho may serve as an early warning sign of the presence of kidney disease and its deadly cardiovascular complications, according to findings by UT Southwestern Medical Center researchers.

Using mice, investigators found that soft-tissue calcification, a common and serious side effect of chronic kidney disease (CKD), improves when Klotho hormone levels are restored. The study is available online in the *Journal of the American Society of Nephrology.*

The essential Klotho protein, which is produced by the kidneys, often plummets in CKD. This may explain why supplementing Klotho levels helps counteract a major side-effect associated with the disease, said Dr. Orson Moe, director of the Charles & Jane Pak Center for Mineral Metabolism and Clinical Research at UT Southwestern and the senior author of the study.

Mice with chronic kidney disease exhibit low levels of Klotho in their kidneys, blood and urine, indicating that CKD is a state of systemic Klotho deficiency, Dr. Moe said. In the study, researchers also tested urine from 53 human participants, including 40 CKD patients, and found that they also had low levels of the essential protein.

"It can be a vicious cycle, where CKD begets low Klotho and low Klotho accelerates CKD," Dr. Moe said. "Chronic kidney disease appears to go hand-in-hand with chronic Klotho deficiency. Animal studies have shown that a dangerous consequence of inadequate Klotho is soft-tissue calcification, which can interfere with normal organ function."

In the current study, UT Southwestern researchers decreased Klotho levels in mice by genetically engineering them to produce inadequate levels of the protein. Restoring adequate Klotho levels to the rodents with CKD markedly improved renal function and blood chemistry and reduced vascular calcification.

In contrast, mice with CKD that were genetically engineered to have abnormally low levels of Klotho had worse kidney function and severe calcification. The beneficial effect of proper Klotho levels on vascular calcification goes beyond the hormone's effect on kidney function, suggesting a direct protective effect of Klotho on the vasculature, Dr. Moe said.

According to the research, Klotho lessens vascular calcification by enhancing the urine's

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phosphate excretions (essential for building and repairing bones and teeth, helping nerve function and making muscles contract, but it can be toxic when levels are high); and preserving kidney fluid filtration. Most importantly, Klotho also appears to inhibit vascular smooth-muscle phosphate uptake and calcification, a complication of CKD that can significantly increase risk of death.

"We tested three hypotheses," Dr. Moe said. "The first was that CKD is a state of Klotho deficiency; the second, that Klotho is an early marker of CKD; and the third, that Klotho deficiency contributes to vascular calcification and Klotho replacement ameliorates CKD via multiple mechanisms. The data we collected seem to bear out all three."

The study's findings also suggest that Klotho replacement therapy may eventually prove to be effective in battling CKD as well as in preventing and reversing its complications.

"It is our hope that this and future research will ultimately lead to better ways to retard the progression of CKD and avoid the dire consequences associated with the disease," Dr. Moe said.

Other UT Southwestern researchers involved in the study were Dr. Ming Chang Hu, instructor of internal medicine and lead author; Dr. Makoto Kuro-o, associate professor of pathology who discovered Klotho more than a decade ago; Mingjun Shi, research associate in internal medicine; Dr. Jianning Zhang, research scientist in internal medicine; Dr. Henry Quinones, assistant professor of internal medicine; and Carolyn Griffith, senior research nurse in mineral metabolism.

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