

Type 2 diabetics' acidity heightens risk for kidney stones

PEOPLE WITH TYPE 2 DIABETES HAVE HIGHLY ACIDIC URINE, A METABOLIC FEATURE THAT EXPLAINS THEIR GREATER RISK FOR DEVELOPING URIC-ACID KIDNEY STONES, RESEARCHERS AT UT SOUTHWESTERN MEDICAL CENTER HAVE FOUND.

Their study, published recently in the *Journal of the American Society of Nephrology*, for the first time compares the urinary biochemical characteristics of type 2 diabetics with those of normal volunteers.

Individuals with type 2 diabetes, also called non-insulin dependent diabetes mellitus, are at increased risk for developing kidney stones in general, and have a particular risk for uric acid stones. The mechanisms for this greater risk were previously not well understood.

This new study demonstrates that the propensity for type 2 diabetics to develop uric acid stones is elevated because their urine is highly acidic.

"Our next step is to find out what causes patients with type 2

diabetes to have abnormally acidic urine, and what urinary factors protect diabetic patients who do not form uric acid stones," said Dr. Mary Ann Cameron, the paper's lead author and an assistant professor of internal medicine.

Obesity and a diet rich in animal protein are associated with abnormally acidic urine. In earlier studies, UT Southwestern researchers also concluded that uric-acid stones are associated with insulin resistance and type 2 diabetes.

But when researchers in this latest study accounted for these components, type 2 diabetics continued to have more acidic urine levels when compared to non-diabetics. These findings suggest that other factors associated with type 2 diabetes or insulin resistance account for the overly acidic urine in this population.

"Diet intake and obesity, those two factors alone, don't explain the whole picture," said Dr. Naim Maalouf, a study author and assistant professor of internal medicine. "So, other unrecognized factors



Cosmetics Inc. Professorship in Mineral Metabolism and Osteoporosis, said: "Our group at UT Southwestern was the first to determine that the more overweight a person is the more likely he or she is to form uric-acid kidney stones."

More than 18 million people in the United States live with diabetes, a chronic disease that affects the body's ability to produce or respond to insulin. It can lead to life-threatening illness, including heart disease and stroke.

Uric-acid stones are more difficult to diagnose than other types of stones because they don't show up on regular abdominal X-rays, often delaying the diagnosis and leading to the continued growth of the stone, Dr. Sakhaee said.

may play a role." Dr. Khashayar Sakhaee, senior author of the study, chief of mineral metabolism and holder of the BeutiControl



The Friends of Mineral Metabolism News is a publication of the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research of UT Southwestern Medical Center.

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F R I E N D S O F

MINERAL METABOLISM

N E W S

UT SOUTHWESTERN
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Clinic earns service in excellence awards ★★★★★

DEBI MOSES BROKE HER HIP WHILE ON A SKI VACATION MORE THAN A DECADE AGO.

During surgery to repair the fracture, her bones shattered. Doctors didn't know why.

Five years ago, she sought the expertise of UT Southwestern Medical Center specialists at the Mineral Metabolism Clinic at the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research.

She visited with Dr. Clarita Odvina, the medical director for the clinic.

"That's when I found out that I had osteoporosis," Mrs. Moses said.

Since then, her condition has improved. Mrs. Moses no longer suffers from osteoporosis. Instead, she has been diagnosed with osteopenia, a condition that refers to having low bone density.



– Dr. Clarita Odvina and patient Debi Moses

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New generation of investigators leads the way

TWO UT SOUTHWESTERN MEDICAL CENTER FACULTY MEMBERS ARE LEADING THE NEXT GENERATION OF PATIENT-ORIENTED RESEARCH AT THE CHARLES AND JANE PAK CENTER FOR MINERAL METABOLISM AND CLINICAL RESEARCH.

Drs. Naim Maalouf and Mary Ann Cameron started out as fellows and spent several years of their postdoctoral fellowships doing research in mineral metabolism

at UT Southwestern. Now, both have accepted jobs as assistant professors in the mineral metabolism division of the internal medicine department.

"I witnessed the growth of both Dr. Maalouf and Dr. Cameron as trainees and was most impressed with their high standards of patient care and medical research. We are most fortunate to retain them here at the Charles and Jane Pak Center," said Dr. Orson Moe,

director of the center and holder of the Charles Pak Distinguished Chair in Mineral Metabolism and the Donald W. Seldin Professorship in Clinical Investigation.

"Both Dr. Maalouf and Dr. Cameron exemplify the triple excellence in academic medicine as clinicians, teachers and researchers. There is no doubt that our patient population will benefit tremendously from their care."

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Dr. Moe's Perspective



DR. ORSON W. MOE

DEAR FRIENDS:
As a new year begins, the transition of Winter to Spring provides a backdrop to reflect on the strong commitment our Center has to the tripartite mission of patient care, education and research. These three activities are not independent but are intimately woven.

Patient care is of paramount importance and it precedes all other endeavors. In this tertiary referral center, we often get the most challenging cases that have baffled other physicians. As stated on the cover of the newsletter, our clinic has enjoyed the honor of Service in Excellence Team Awards, which reflect the highest patient satisfaction. I cannot overstate how gratifying that is. In addition to deriving satisfaction out of seeing our patients get better, our physicians often use these cases as teaching materials as well as starting points to launch research projects.

On the teaching front, we have trained specialists in mineral metabolism and witnessed some of them commence their own careers elsewhere. It is rewarding to see that they will spread the knowledge and philosophy from our center. We are fortunate to retain Drs. Maalouf and Cameron, who will share our missions and duties in the years ahead.

Numerous research projects are moving steadily forward. The study on kidney-stone risk in patients taking Topamax is an example of research that came straight out of the clinic. As I participated in national and international meetings in mineral research in the past year, I felt great pride and satisfaction to see our faculty poised in pivotal positions in the research community.

The research on uric-acid stones covered in this newsletter is an example where the UT Southwestern mineral group has led, and continues to lead, the entire front of progress. This work also was inspired by patients in our practice over the years.

Our faculty and staff are committed to fulfill the missions of patient care, teaching and research. We will strive to further improve our practice, take education to higher grounds and train more physicians and scientists, and conduct clinical and basic research of the highest quality possible. All these activities stem from patients, and it is our duty to bring the outcome back to the benefit of the patients. We are most grateful for the support of our patients and donors who share our views and we look forward to serving and working with our *Friends of Mineral Metabolism*.

ORSON W. MOE, M.D.
DIRECTOR OF THE CHARLES AND JANE PAK
CENTER FOR MINERAL METABOLISM AND
CLINICAL RESEARCH



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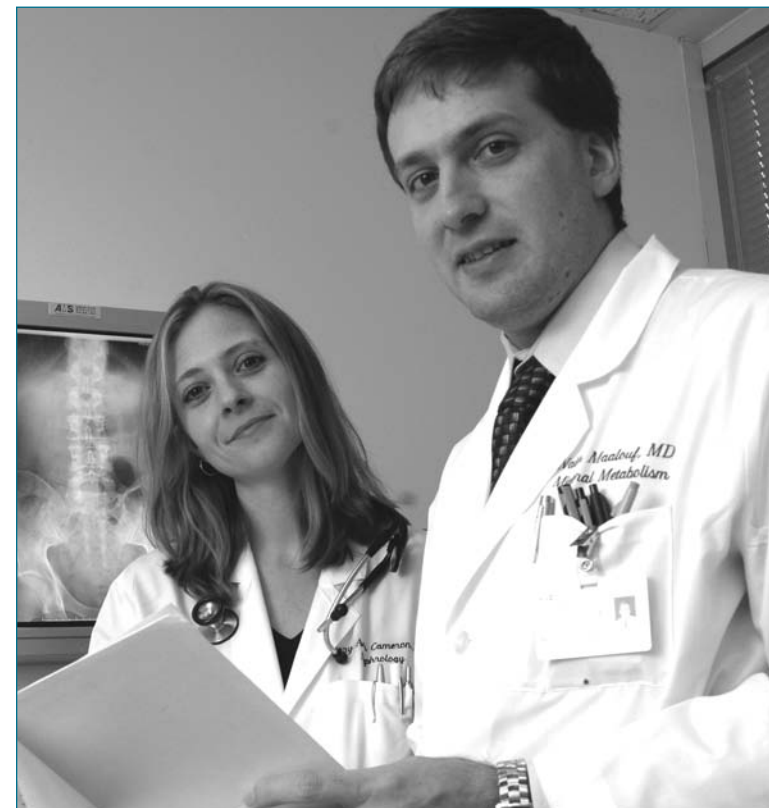
FELLOWS

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Olivier Bonny, M.D., Ph.D.

The Mineral Metabolism Clinic specializes in various mineral metabolism diseases such as osteoporosis, osteomalacia, Paget's disease, hyperparathyroidism, acid base bone metabolism, nephrolithiasis, kidney-stone disease and prevention, and calcium disorders.

Patients are seen on a referral basis. Please have your primary care physician contact our clinic at 214-645-2870 to schedule an appointment with one of our specialists.

The Mineral Metabolism Clinic is located in the James W. Aston Ambulatory Care Center at 5303 Harry Hines Blvd., Dallas.



– Drs. Mary Ann Cameron and Naim Maalouf

INVESTIGATORS

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Dr. Moe also said: "It is unlikely that our trainees will encounter better teachers. I am looking forward to seeing both of them evolve into medical researchers of international stature."

Dr. Maalouf received his medical degree from the American University of Beirut. He completed a residency in internal medicine at Emory University.

He joined UT Southwestern in 2001 as a fellow in endocrinology and spent his first year treating patients with diabetes and other endocrine problems.

As a researcher, he has studied the relationship between body weight and uric acid kidney stones, which are prevalent in individuals with type 2 diabetes, also called non-insulin

dependent diabetes mellitus.

"The studies on kidney stones in patients with type 2 diabetes is where I started," Dr. Maalouf said. "It was a good way for me to bridge the research between endocrinology and mineral metabolism."

In addition to studies on kidney stones, Dr. Maalouf is interested in osteoporosis research. He has published research in several journals and recently received a five-year, \$500,000 grant from the National Institutes of Health to study the mechanism by which high-protein diets increase the risk of bone loss and stone formation.

Dr. Maalouf also sees patients with kidney stones and osteoporosis at the Mineral Metabolism Clinic in the James W. Aston Ambulatory Care Center.

Dr. Cameron earned her medical

degree and completed her residency at Baylor College of Medicine in Houston. She came to UT Southwestern in 2002 as a fellow to specialize in nephrology.

She became a faculty member in October and has dual appointments in the divisions of mineral metabolism and nephrology.

As a fellow, she received a National Kidney Foundation fellowship grant to support her research into how uric acid kidney stones develop.

In 2005, she was one of 12 UT Southwestern researchers chosen as the first group of young investigators to participate in the Clinical Scholars Program.

As a clinical scholar, Dr. Cameron spends 75 percent of her time in an intense three-year educational and training program to prepare her for a career as an independent clinical investigator.

Her research interests include studying the effects of insulin resistance on renal physiology, specifically on the development of acidic urine and uric acid stones, as well as hypertension.

Dr. Cameron also sees patients at the Mineral Metabolism Clinic at the Aston Center and supervises fellows during their rotations in nephrology.

"I have performed patient oriented research over the past three years in the Center for Mineral Metabolism. It has been an excellent experience that allows me to study the pathophysiology of kidney stones with the goal of providing new treatment options," Dr. Cameron said. "I enjoy working with our volunteers whose interest and dedication is essential for these studies, as well as with our supportive staff. I look forward to developing and performing future studies at the center."

Osteoporosis is increasingly becoming a man's disease, too

OSTEOPOROSIS IS COMMONLY THOUGHT OF AS A WOMAN'S HEALTH PROBLEM, BUT IT IS INCREASINGLY BECOMING A MAN'S HEALTH ISSUE, TOO.

Although it strikes more women than men – of the 10 million Americans estimated to have osteoporosis, 8 million of them are women and 2 million are men – the disease is more likely to go undiagnosed in men.

Dr. Khashayar Sakhaee, chief of the division of mineral metabolism, a member of the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, and holder of the BeautiControl Cosmetics Inc. Professorship in Mineral Metabolism and Osteoporosis, discusses the disease and offers some recommendations.

Q: WHY IS OSTEOPOROSIS LESS COMMON IN MEN THAN IN WOMEN AND HOW DOES IT DIFFER BETWEEN THE SEXES?

Dr. Sakhaee: Men generally have larger and stronger bones than women. They also don't experience the hormonal changes that women do after menopause. The pattern of bone loss is also different in men: It begins later in life and advances more slowly.

Q: HOW IS OSTEOPOROSIS DIAGNOSED? WHAT TYPE OF TESTS SHOULD BE DONE?

Dr. Sakhaee: Bone mineral density measurement is the first step in the diagnosis of osteoporosis in men, just as it is in women. If the patient's bone mineral density is found to be significantly below young normal mean, the next step would be to measure blood levels of testosterone, vitamin D and parathyroid hormone,



– Dr. Khashayar Sakhaee

as well as to check the level of calcium in the patient's urine, which is an indicator of bone loss.

Q: WHO SHOULD BE TESTED?

Dr. Sakhaee: Men with a history of fractures and long-term users of certain medications, such as steroids, anti-convulsants and certain cancer treatments, should be evaluated. Those with a family history of osteoporosis, chronic gastrointestinal or liver diseases, and renal impairment should also be tested, as should smokers and excessive alcohol users.

Q: WHAT IS THE TREATMENT AND WHAT CAN MEN DO TO TRY TO PREVENT OR LIVE WITH OSTEOPOROSIS?

Dr. Sakhaee: Lifestyle modifications such as abstinence from smoking, moderate alcohol intake, regular physical exercise and specific attention to underlying conditions are important. Adequate calcium intake is essential. In general, men aged 30 to 50 should take 1,000 milligrams of calcium daily and 1,200 milligrams after age 50. Vitamin D is also important. In men 50 to 70 years old, 400 to 800 international units (IU) of vitamin D may be sufficient, but the dose should increase after age 70. An annual bone mineral density analysis and blood and urine tests are also good ways to try to prevent the disease.

A pack of Pak Awards

Several employees in the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research were honored in 2006 with the Charles and Jane Pak Awards. The Pak awards are given twice each year in recognition of outstanding efforts to achieve and maintain excellence in all aspects of the center's operations.

The most recent winners, recognized in November 2006, are: **Kathy Hill**, a research associate; and **Mary "Kitty" Jackson**, a cook in the General Clinical Research Center.

The May 2006 Pak Award winners are: **Beverly Kemp**, clinical staff supervisor; **Paulette Padalino**, research scientist, and; **Trevor Henderson**, technical support specialist.

■ ■ ■

"THE TWO MOST CRITICAL ELEMENTS OF A GOOD CLINICAL PRACTICE ARE OUTSTANDING MEDICAL EXPERTISE AND PASSIONATE DEDICATION TO PATIENT CARE. ONE WITHOUT THE OTHER WILL SIMPLY NOT SUFFICE."

– DR. ORSON MOE,
DIRECTOR OF THE CHARLES AND JANE PAK
CENTER FOR MINERAL METABOLISM
AND CLINICAL RESEARCH

CLINIC

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It is less severe than osteoporosis and she has not had any additional fractures.

"If you know you have this, there's no reason not to be proactive about it," said Mrs. Moses. "And there is no one else I'd go see for treatment."

Many other patients share Mrs. Moses' respect and affection for the doctors and staff at the Mineral Metabolism Clinic.

Since 2004, the clinic has received four Service in Excellence Team Awards from UT Southwestern recognizing excellence in patient satisfaction.

UT Southwestern randomly surveys patients about their experience at all campus clinics. In order to be recognized for excellence, the clinics must receive a score in the 90th percentile.

"Taking care of patients is our priority," Dr. Odvina said. "When we receive compliments from our patients, it absolutely reaffirms our commitment to serve them."

In addition to the physicians, the clinic staff includes two nurses, a medical office assistant, a clerical assistant and two bone-density technicians.

"Many patients suffer with kidney stones or osteoporosis for years before they come here, after no one had been able to help them," said Kimberly Jackson, the clinic's nursing supervisor. "Once they get here, they know that whatever condition or ailment they have, it will be taken care of."

Mrs. Jackson, who is also a research nurse, said many patients are long-term visitors to the clinic and have established relationships with their doctors. Those patients include Mrs. Moses, who has given up skiing but remains physically active. She visits Dr. Odvina every

"TAKING CARE OF PATIENTS IS OUR PRIORITY. WHEN WE RECEIVE COMPLIMENTS FROM OUR PATIENTS, IT ABSOLUTELY REAFFIRMS OUR COMMITMENT TO SERVE THEM."

– DR. CLARITA ODVINA

six months for follow-up exams.

"Some patients have been with us since the start and they have watched the clinic grow," Mrs. Jackson said.

Dr. Charles Y.C. Pak established the Center for Mineral Metabolism and Clinical Research at UT Southwestern in the early 1970s. In 2004, the center was renamed to honor his decades of contributions to the medical center.

The Center oversees the Mineral Metabolism Clinic and coordinates the activities of the National Institutes of Health-funded General Clinical Research Center.

"The two most critical elements of a good clinical practice are outstanding medical expertise and passionate dedication to patient care. One without the other will simply not suffice," said Dr. Orson Moe, director of the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research and holder of the Charles and Jane Pak Distinguished Chair in Mineral Metabolism and Donald W. Seldin Professorship in Clinical Investigation.

"The experience of Mrs. Moses exemplifies both features at the Mineral Metabolism Clinic. I congratulate the staff of our clinic for their performance and I am proud to be their associate," he added.

Brinkley retires after more than three decades



– Linda Brinkley

WHEN LINDA BRINKLEY STARTED WORKING AS A RESEARCH DIETITIAN AT THE GENERAL CLINICAL RESEARCH CENTER (GCRC) IN 1973, DIETS FOR RESEARCH SUBJECTS WERE CALCULATED WITH A PENCIL, PAPER AND A CALCULATOR.

Some days, it would take half a day to determine the proper diets for Dr. Charles Y.C. Pak's research subjects or those of his investigators.

Nowadays, diets are calculated with a few computer keystrokes, in a quarter of the time.

But Ms. Brinkley, a registered dietitian, is no longer doing those calculations or serving as the "resident historian." After more than three decades in the department, she retired in February.

"The hardest thing is leaving the people that I work with," Ms. Brinkley said. "I really enjoy them and we've gotten to know each other pretty well over the years."

As a research dietitian, Ms. Brinkley has helped investigators develop diets so that they can obtain accurate data from the

patient groups being evaluated.

In the research kitchen, she oversees the cooks to ensure they prepare the foods by following strict guidelines so that the research diets don't interfere with what investigators are trying to determine when testing medications or treatments.

"When viewed in the time course of Ms. Brinkley's career, I came in rather late in the picture. Ms. Brinkley was publishing in medical journals with Dr. Pak while I

was still in medical school," said Dr. Orson Moe, director of the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research and holder of the Charles Pak Distinguished Chair in Mineral Metabolism and Donald W. Seldin Professorship in Clinical Investigation.

"Ms. Brinkley is an integral part of the history of our center. It is no exaggeration when I state that Ms. Brinkley's contribution to our center and to mineral metabolism research in general has been significant over the years. There are few individuals in this field who have such in-depth knowledge of dietetics. Her departure will be missed by the faculty, the staff and the patient subjects."

Ms. Brinkley received a bachelor's degree from North Texas State University in 1965 and completed a dietetic internship at the Medical College of Virginia in Richmond.

A native Texan, she returned to Dallas after her internship and started working at Parkland Memorial Hospital as a clinical dietitian. She also took graduate courses at Texas Woman's University.

Dr. Pak arrived at UT Southwestern

Medical Center in 1972 and hired Ms. Brinkley in 1973. He was one of the UT Southwestern faculty members utilizing the National Institutes of Health-funded General Clinical Research Center. He later established the Center for Mineral Metabolism and Clinical Research, under which the GCRC operates. The Center for Mineral Metabolism and Clinical Research was named in Dr. Pak's honor in 2004.

Ms. Brinkley is one of several staff members hired by Dr. Pak who have spent the rest of their medical careers working for him.

"We all developed good working relationships over time," Ms. Brinkley said. "I'm the only dietitian, but I don't feel isolated from the rest of the unit – the nurses, the people that work in the lab, the administrators. We're all part of the same team and that's the only way to get anything done – through teamwork."

When Ms. Brinkley first started, the GCRC and her research kitchen were still under construction.

"We were doing things piecemeal in temporary facilities and we were spread out all over the place," Ms. Brinkley recalled.

The opening of the center is one of the highlights of her career, she said. The center's first federal grant renewal allowed her to achieve a personal goal – the purchase of her first home.

"I waited five years, until the center's first grant was renewed, to buy my house," Ms. Brinkley said. "I wanted to make sure that I had a job."

Through the years, Ms. Brinkley has enjoyed watching the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research and the GCRC grow into world-renowned research centers. She has also witnessed the field of dietetics evolve.

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Calcium intake a factor in formation of kidney stones

INDIVIDUALS WITH EITHER CALCIUM OXALATE OR CALCIUM PHOSPHATE KIDNEY STONES SHOULD NOT TAKE EXTRA CALCIUM ON THEIR OWN AS SUGGESTED BY PREVIOUS RESEARCH, BUT SHOULD CHECK WITH THEIR DOCTORS TO DETERMINE THE DIETARY GUIDELINES THAT WORK BEST FOR THEM, RESEARCHERS AT UT SOUTHWESTERN MEDICAL CENTER HAVE FOUND.

Urinary calcium – the amount of calcium in a person's urine – is an important contributing factor in the formation of both types of kidney stones. Earlier studies had downplayed the significance of calcium when compared to the levels of oxalate in urine, and even encouraged kidney stone patients to increase their dietary intake of calcium.

"We often see patients who tell us they have been advised to take more calcium; however, that could be a dangerous recommendation for some individuals," said Dr. Margaret Pearle, professor of urology and holder of the Dr. Ralph C. Smith Distinguished Chair in Urologic Education at UT Southwestern. She and her colleagues published their findings about calcium in two studies in *Kidney International* and the *Journal of Urology*.

"While we want to be cautious in

asking anyone to restrict calcium intake because of the risk of bone disease, we also realize that urinary calcium has about the same influence as urinary oxalate in calcium oxalate stone formation, and we may want to recommend calcium restriction in patients who have moderately to severely elevated intestinal calcium absorption and urinary calcium levels," she said.

The same is true for patients with calcium phosphate stones, said Beverley Adams-Huet, a faculty associate in internal medicine and a biostatistician in UT Southwestern's General Clinical Research Center (GCRC).

"Our research shows that the level of urinary calcium also has an important influence in the formation of calcium phosphate stones," she said. "Both of these studies offer supportive evidence that people with calcium phosphate stones may need to carefully monitor their calcium dietary intake."

The most common type of kidney stone contains calcium in combination with either oxalate or phosphate, with calcium oxalate stones accounting for about 60 percent and calcium phosphate about 20 percent of kidney stones.

Calcium was not regarded as important as oxalate in kidney-stone

formation in earlier studies because a different "stability constant," or mathematical formula, was used to calculate urinary saturation of calcium oxalate, with results showing that less attention should be focused on calcium. Researchers at UT Southwestern, however, used a newer, lower stability constant, today regarded as the "gold standard" in the industry, yielding data that pointed to calcium's more essential role.

Dr. Charles Y.C. Pak, former director of the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, urges patients to seek their physician's advice before deciding whether to limit or increase calcium in their diets.

"For the patient, the message of these studies is that the recommendation for calcium intake cannot be generalized because the effect of calcium intake on stone formation depends on the type of stone, oxalate intake, presence of stones and the efficiency of calcium absorption from the bowel," Dr. Pak said.

"Our future challenge is to understand various factors that modify the effect of calcium restriction on urinary calcium and stone-forming propensity, and to determine how best to use diet and drugs to control high urinary calcium and stone formation."



BRINKLEY

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For example, when she first started, research patients would spend weeks living in the inpatient facility of the GCRC. Now, for many studies, the foods are packaged and sent home with them.

In 1981, Ms. Brinkley became the administrative manager of the GCRC, but she returned to her previous post after seven years because she missed

dietetics, the action of implementing protocols and dealing with the nutritional needs of patients.

"The thing that kept me going all these years is that there is always something new going on all the time," Ms. Brinkley said. "New investigators, new studies, new things to learn."

And she's excited about the new adventures that retirement will bring.

Ms. Brinkley developed an interest in genealogy several years ago and is

researching her family tree.

She and her mother have traveled to Arkansas, Tennessee and various sites in Texas and Georgia to visit graveyards, libraries, courthouses and archives. She also enjoys photography.

"I like to take pictures, which goes along with the genealogy and the traveling," Ms. Brinkley said. "I have enough hobbies to last me for the next 30 years."



Drug for migraines and seizures increases risk of kidney stones

TOPIRAMATE (TOPAMAX), A DRUG COMMONLY PRESCRIBED TO TREAT SEIZURES AND MIGRAINE HEADACHES, CAN INCREASE THE PROPENSITY OF CALCIUM PHOSPHATE KIDNEY STONES, RESEARCHERS AT UT SOUTHWESTERN MEDICAL CENTER HAVE FOUND.

A study – the largest cross-sectional examination of how long-term use of topiramate affects kidney-stone formation – was published recently in the *American Journal of Kidney Diseases*.

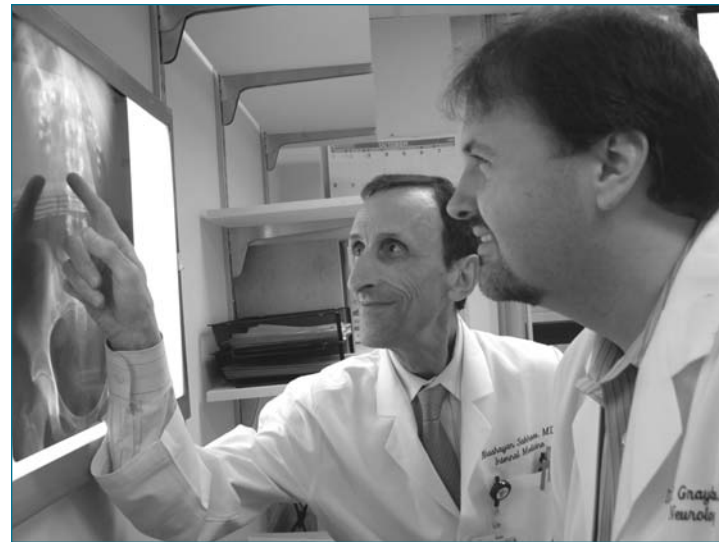
Several case reports have described an association between topiramate and the development of kidney stones, but this complication had not been well recognized and physicians have not informed patients about the risk, the UT Southwestern researchers said. More important, the mechanism of stone formation was largely unknown previously.

“The wide-spread and escalating use of topiramate emphasizes the importance of considering the long-term impact of this drug on kidney-stone formation,” said Dr. Khashayar Sakhaee, senior author of the study, chief of mineral metabolism at UT Southwestern and holder of the BeautiControl Cosmetics Inc. Professorship in Mineral Metabolism and Osteoporosis.

More than 29 million Americans suffer from migraines, with women being affected three times more often than men, according to the National Headache Foundation.

“Topiramate is probably one of the most commonly prescribed and most effective neurological medications right now,” said Dr. Dion Graybeal, assistant professor of neurology and a study author.

Dr. Graybeal and other researchers at UT Southwestern say the next step is to develop a way to block the development of kidney stones for topiramate users.



– Drs. Khashayar Sakhaee and Dion Graybeal

The study comprised two phases. Thirty-two individuals already being treated with topiramate and 50 normal volunteers were enrolled in a cross-sectional study in which their blood and urine were tested for kidney-stone risk. A short-term study also was conducted in seven individuals to assess stone risk before and three months after taking topiramate. All patients were evaluated at UT Southwestern’s General Clinical Research Center.

Researchers found that taking topiramate on a long-term basis, or for about one year, caused systemic metabolic acidosis – a buildup of excessive acid in the blood – as a result of the inability of the kidney to excrete acid. Topiramate use also increased the urine pH and lowered urine citrate, an important inhibitor of kidney-stone formation.

“These changes increase the propensity to form calcium phosphate stones,” Dr. Sakhaee said.

In the short-term study, urinary calcium and oxalate – a chemical compound that binds strongly with calcium and is found in most calcium stones – did not significantly change in people taking topiramate.

Kidney stones are solid deposits

that form in the kidneys from substances excreted in the urine. When waste materials in urine do not dissolve completely, microscopic particles begin to form and, over time, grow into kidney stones.

Before this study, the rate of kidney-stone formation with topiramate was reported as 1.5 percent. The low incidence rate may be an underestimation due to the short length of observation and the lack of ongoing kidney-stone surveillance and data collection for this drug, Dr. Sakhaee said.

“There is a legitimate concern for the occurrence of kidney stones with long-term topiramate treatment,” Dr. Sakhaee said. “Studies are needed to explore optimal measures to prevent kidney-stone formation with topiramate use.”

Other UT Southwestern researchers contributing to the study were Drs. Orson Moe, director of the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, Naim Maalouf, assistant professor of internal medicine, and Brian J. Welch, a postdoctoral fellow in internal medicine.

The research was supported by the National Institutes of Health.

OJ is better than lemonade at keeping kidney stones away

A DAILY GLASS OF ORANGE JUICE CAN HELP PREVENT THE RECURRENCE OF KIDNEY STONES BETTER THAN OTHER CITRUS FRUIT JUICES SUCH AS LEMONADE, A RESEARCHER AT UT SOUTHWESTERN MEDICAL CENTER HAS DISCOVERED.

The study, published in the *Clinical Journal of the American Society of Nephrology*, indicates that although many people assume that all citrus fruit juices help prevent the formation of kidney stones, not all have the same effect.

Medically managing recurrent kidney stones requires dietary and lifestyle changes as well as treatment such as the addition of potassium citrate, which has been shown to lower the rate of new stone formation in patients with kidney stones.

But some patients can’t tolerate potassium citrate because of gastrointestinal side effects, said Dr. Clarita Odvina, associate professor of internal medicine at the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research and the study’s lead author. In those cases, dietary sources of citrate – such as orange juice – may be considered as an alternative to pharmacological drugs.

“Orange juice could potentially play an important role in the management of kidney-stone disease and may be considered an option for patients who are intolerant of potassium citrate,” Dr. Odvina said.

All citrus juices contain citrate, a negatively charged form of citric acid that gives a sour taste to citrus fruits. Researchers compared orange juice and lemonade – juices with comparable citrate contents – and found that the components that accompany the citrate can alter the effectiveness of the juice in decreasing the risk of developing new kidney stones.

Kidney stones develop when the urine is too concentrated, causing

minerals and other chemicals in the urine to bind together. Over time, these crystals combine and grow into a stone.

In the UT Southwestern study, 13 volunteers – some with a history of kidney stones and some without – underwent three phases, each lasting one week. Chosen in random order, the phases included: a distilled water or control phase; an orange juice phase; and a lemonade phase. There was a three-week interval between phases.

During each phase, volunteers drank 13 ounces of orange juice, lemonade or distilled water three times a day with meals. They also maintained a low-calcium, low-oxalate diet. Urine and blood samples were taken at intervals during each phase. The study was done at UT Southwestern’s General Clinical Research Center.

Orange juice, researchers found, boosted the levels of citrate in the

urine and reduced the crystallization of uric acid and calcium oxalate – the most frequently found ingredient in kidney stones.

But lemonade did not increase the levels of citrate, an important acid neutralizer and inhibitor of kidney-stone formation.

“One reason might be the different constituents of various beverages,” Dr. Odvina said.

For instance, the citrate in orange and grapefruit juice is accompanied by a potassium ion, which has a negative electronic charge, while the citrate in lemonade and cranberry juice is accompanied by a hydrogen ion, which has a positive charge. Ions of hydrogen, but not potassium, counteract the beneficial effects of the high citrate content.

“There is an absolute need to consider the accompanying positive charge [of hydrogen ions] whenever one assesses the citrate content of a diet,” Dr. Odvina said.



“ORANGE JUICE COULD POTENTIALLY PLAY AN IMPORTANT ROLE IN THE MANAGEMENT OF KIDNEY-STONE DISEASE.”

– DR. CLARITA ODVINA



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News you can use

The best bones are those that get a workout

Exercise can help people with osteoporosis stay fit and improve their balance. The best exercises for the bones are weight-bearing activities such as walking, dancing, jogging, hiking, tennis or stair climbing.

"Exercise helps to increase or preserve bone mass and strengthen muscles, which improves balance and can prevent falls," said Dr. Naim Maalouf, assistant professor of internal medicine.

If you've been sedentary for any length of time, be sure to consult with your doctor before starting an exercise program.

Kidney stones – painful, but perhaps preventable

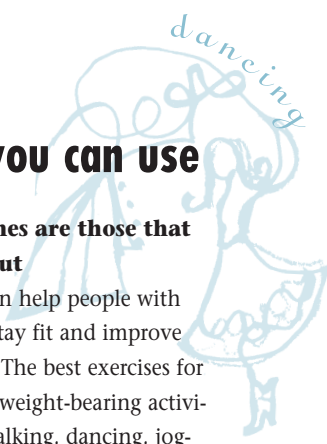
Kidney stones are one of life's more painful disorders and their discovery in a 7,000-year-old Egyptian mummy shows they have been with us since ancient times.

Modern lifestyles, however, can exacerbate kidney stones, which can contain a variety of substances, most commonly calcium and uric acid.

Dr. Orson Moe, director of the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, said there are ways to prevent kidney stones from forming.

In general, drink up to 12 full glasses of water daily to help dilute or flush away substances that form stones, he said. Also, avoid excessive protein intake to reduce the risk.

Dr. Moe said signs of a possible kidney stone include extreme pain in the back or side that will not go away, blood in the urine, fever and chills, vomiting, urine that smells bad or looks cloudy, and a burning feeling during urination. If you experience any of these symptoms, see your physician as soon as possible.



NOTES

Dr. Alireza Atef-Zafarmand, formerly a resident in internal medicine at Wayne State University in Michigan, began a postdoctoral fellowship in nephrology at UT Southwestern in 2004 and in mineral metabolism in 2005. Currently, he is working with Dr. Khashayar Sakhaee and Dr. Orson Moe on several projects, including the investigation of post-renal transplant hyperphosphaturia and different techniques for measuring gastrointestinal calcium absorption.

Dr. Olivier Bonny received his M.D. and Ph.D. from the University of Lausanne in Switzerland. After completing his postgraduate training in internal medicine and nephrology, he has joined the laboratory of Dr. Orson Moe to conduct basic research in regulation of calcium handling by the kidney. Dr. Bonny has received grant support from the Swiss National Science Foundation and the National Kidney Foundation. He studies a protein in the

kidney called the sodium-calcium exchange which has major roles in determining how the kidney handles calcium.

Dr. Damaris Vega, who received her medical degree in 2002 from Ponce School of Medicine in Puerto Rico and completed a residency in internal medicine at UT Southwestern, has started a postdoctoral fellowship in mineral metabolism. Dr. Vega will assist Dr. Khashayar Sakhaee in his studies comparing potassium citrate and citric acid supplements for patients being treated with topiramate, a drug commonly prescribed for the treatment of seizures and migraine headaches.

Researchers in the biotechnology program within the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research are involved in a collaborative study with the Henry Ford Hospital in Detroit to measure bone quality by using ultrasound. This non-invasive technique has the potential to safely measure cortical and trabecular bone strength.

Dr. David Baylink, a world-renowned expert in osteoporosis and a professor of medicine at Loma Linda University, visited UT Southwestern to discuss new treatment methods for osteoporosis as part of the Lillian B. Clark Lecture Series in Mineral Metabolism.

Three staff members joined the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research since July. Gail Cook is a senior administrative assistant, Amy Fitts is an administrative assistant and Miranda King is a clinical research coordinator.

Roy Peterson, who came to work for Dr. Charles Y.C. Pak in 1973, retired in June 2006. Mr. Peterson's main duties were to coordinate and monitor clinical studies for the Center for Mineral Metabolism and Clinical Research. Since his retirement, Mr. Peterson has been returning to work one day a week to attend meetings and work on special projects for Dr. Pak. He also continues to monitor some studies.



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