

Study links common male medical condition, vascular disease

By Nicoletta Lanese

Men who suffer symptoms from varicoceles, enlarged veins in the scrotum, are more likely to develop vascular disease and metabolic disease, such as diabetes, according to a study by School of Medicine researchers.

Michael Eisenberg, MD, assistant professor of urology, and his team mined data from thousands of medical insurance records to see whether the condition, previously linked to infertility, also puts men at higher risk for other health problems.

Their findings were published online Dec. 1 in *Andrology*. Eisenberg is the senior author. Urology resident Nancy Wang, MD, is the lead author.

About 15 percent of American men are estimated to have varicoceles, dilated veins in the scrotum. The condition is linked to lower sperm levels and testosterone production. It also can cause pain or shrinkage of the testicles, but often results in none of these symptoms and is left untreated.

"To millions of men that are diagnosed with this, a lot of them are told, 'Don't worry about it,'" Eisenberg said.

Varicoceles are treated for infertility and pain, but other risks may be going unchecked. "Varicoceles are associated with low testosterone, and low testosterone in turn is associated with metabolic risks and heart disease," Wang said. No one has connected the dots between varicoceles, testosterone and these conditions before now, she said.

A strong correlation

For the study, Eisenberg's lab dug through a wealth of data housed in the Truven Health Marketscan Commercial Claims and Encounters database, which contains insurance claims filed by 77 million individuals since 1996. Between 2001 and 2009, the researchers identified more than 4,400 reproductive-age men with diagnosed varicoceles. For comparison, the team also looked at men without varicoceles — a group that included both infertile and fertile men, differentiated based on whether they had received infertility screening or a vasectomy.

The team followed the subjects through time, noting their health status up to about three years out from their diagnoses. They monitored whether the men developed metabolic or vascular disorders.

Compared to men without varicoceles, men with the condition had a significantly higher incidence of heart disease, the researchers found. They also had a higher

incidence of diabetes and hyperlipidemia, or high concentrations of fat in their blood.

For the most part, only symptomatic varicoceles are treated in the clinic. Asymptomatic varicoceles — those that don't cause pain or impair reproductive function — are only monitored. But the researchers wondered whether both types increase men's risk of developing other diseases and decided to look closer at the data to answer this question.

"The development of these diseases is usually pretty silent."

The team categorized the men with varicoceles by the symptoms they showed, if any, and found that men with asymptomatic varicoceles had no increase in their incidence of heart disease, diabetes or hyperlipidemia relative to men without varicoceles. Only men with symptoms, especially fertility problems and scrotal pain, showed increased risk of developing these diseases.

The results suggest that monitoring for asymptomatic varicoceles remains reasonable, said Eisenberg. "If it's truly asymptomatic, observation remains appropriate," he said.

Although the study produced strong results, it also had limitations, the researchers wrote. The MarketScan Database collects data from a subset of privately insured individuals and may not represent all American men. Those diagnosed with varicoceles are known to have sought out specialist care, which constricts the sample further. In addition, the data lack details about how the varicoceles were diagnosed and how specific symptoms were recorded, and follow-up data was limited to a few years after diagnosis; disease development beyond that window was not available.

In the last few decades, the rates of cardiac, metabolic and vascular diseases have increased across the United States. This study holds out the possibility that varicoceles may provide a window into men's future health.

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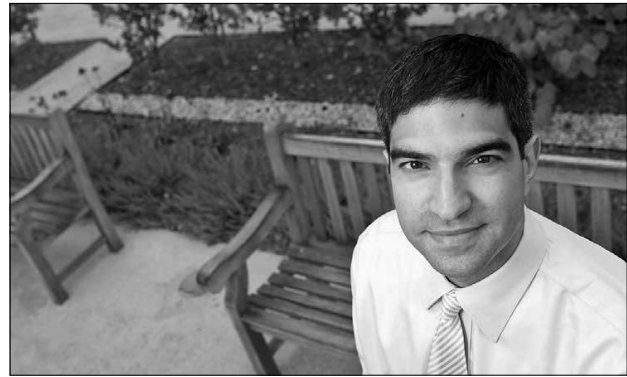
silent," Wang said. "It's interesting to think about ways to catch disease early, or see risk factors you can identify, to prevent their development or progression."

Going forward, Eisenberg hopes to determine the specific role of varicoceles in metabolic and vascular disease. He said he has uncovered a strong correlation but needs to dig deeper to know if varicoceles play a causative role in these conditions. If they do, the question becomes whether varicocele treatment could help prevent later disease.

"While these results make a strong case that varicoceles are associated with higher risks of cardiovascular diseases and diabetes, we do not yet know if we will need to change our present management for the estimated 17 million U.S. men with varicoceles," said Keith Jarvi, MD, director of the Murray Koffler Urologic Wellness Centre and head of urology at Mount Sinai Hospital in Toronto, who was not involved with the study. "The big question is, 'Is a varicocele just a marker of men's health or could repair of the varicocele actually improve men's health in the long term?'"

Other Stanford co-authors of the study are urology

STEVE FISCH



Michael Eisenberg and his colleagues found that men who have symptoms associated with enlarged veins in their scrotums are more likely to develop vascular and metabolic disease.

resident Kai Dallas, MD; Laurence Baker, PhD, professor of health research and policy; and statistical programmer Shufeng Li.

The study did not receive outside funding. Stanford's Department of Urology helped to support the work. **ISM**

Gut

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Over the past 15 years, researchers have shown that the composition of a person's gut microbiome can alter their risk for all sorts of health problems, from diabetes and heart disease to allergies and depression.

One reason these tiny microbes have such an outsized effect: They can produce molecules known as metabolites that enter the bloodstream and circulate throughout the body. Pinning down exactly which molecules are produced by which bacteria, however, and how to alter their levels to change health, has been challenging.

Improving health from the inside

Previous studies have shown that just a few bacteria, including *C. sporogenes*, can break down tryptophan and produce the metabolite known as indolepropionic acid. Studies have also hinted that IPA helps fortify the intestinal wall, letting fewer molecules leak through.

In the new work, the researchers first detailed exactly how *C. sporogenes* produces IPA from tryptophan. They identified a handful of other compounds also produced in the process — 12 metabolites in total, nine of which can accumulate in the blood and three of which



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are produced only by bacteria. Then, the researchers pinpointed for the first time the genes that *C. sporogenes* requires for the breakdown of tryptophan and metabolism of the resulting molecules. A gene called *fldC*, they showed, is required for the production of IPA.

Next, the team gave germ-free mice either wild-type *C. sporogenes* — with the ability to produce IPA — or a version of the bacteria that lacked *fldC*. In mice that received the wild-type bacteria, levels of IPA in the bloodstream were around 80 micromolar; in mice that received the engineered version of the bacteria, IPA was undetectable.

Finally, they looked at how altering the levels of IPA affected the mice. Mice with undetectable IPA, they found, had higher levels of immune cells, including neutrophils, classical monocytes and memory T cells. This suggested activation of two branches of the immune system — the innate and adaptive immune system. In addition, the mice with the engineered version of *C. sporogenes* had

more permeable intestines, a defect which is often seen in gut diseases, including inflammatory bowel disease.

Targeting microbes

If the results hold true in humans, said Sonnenburg, it could point toward a new paradigm for treating some diseases: rather than give a compound, such as IPA, physicians may one day be able to tweak levels of bacteria to affect levels of metabolites. For instance, it might be possible to treat inflammatory bowel disease by boosting levels of *C. sporogenes* and ensuring patients eat enough tryptophan.

"This gives us a specific example of how we can target individual microbes and pathways in the gut to change a person's health," Dodd said. "And this is just one example of hundreds or thousands that are likely out there."

The group next plans to study *C. sporogenes* and IPA levels in mice with more complex gut microbiomes — rather than germ-free mice — and begin tracking down other metabolites produced by the gut microbes that may have health effects.

"While providing a stunning example of how a single gut microbe, and a single gene within that microbe, can impact host health, IPA is just the tip of the iceberg," said Fischbach. "The possibility to positively impact human health through microbiome-produced chemicals is tremendous, and we are poised to take big strides and make this a reality."

Other Stanford authors are Matthew Spitzer, PhD, a former graduate student; graduate students William Van Treuren and Bryan Merrill; postdoctoral scholar Andrew Hryckowian, PhD; life science researcher Steven Higginbottom, PhD; Gary Nolan, PhD, professor of microbiology and immunology; adjunct faculty member Anthony Le; and Tina Cowan, PhD, professor of pathology.

Sonnenburg and Fischbach are both members of Stanford ChEM-H.

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