Persistent Acid Reflux And Cancer

New research from the University of Texas Southwestern Medical School and the Dallas Veterans Affairs Medical Center underscores the importance of preventing recurring acid reflux. The studies have also uncovered clues on how typical acid reflux can turn potentially cancerous.

People with a complication of acid reflux disease called Barrett’s esophagus have altered cells in the esophagus. These cells contain shortened telomeres, the ending sequences in DNA strands. Shortened sequences seem to allow other cells more prone to cancer to take over.

Dr. Rhonda Souza, Associate Professor of Internal Medicine at the university, explains:

"The research supports why it is important to prevent reflux, because the more reflux you have and the longer you have it, the more it might predispose you to getting Barrett’s esophagus. So you want to suppress that reflux."

Heartburn occurs when acid splashes back up from the stomach into the esophagus, causing a burning sensation. Over time, the persistent acid bath can cause normal epithelial cells in the esophagus to change into tougher, more acid-resistant cells of the type found in the stomach and intestine, explained Dr. Stuart Spechler, Professor of Internal Medicine and senior author of the paper.

"Unfortunately, those acid-resistant cells are also more prone to cancer," he said.

Adenocarcinoma of the esophagus, a cancer that is commonly associated with Barrett’s esophagus, is the most rapidly rising cancer in the United States; it has shown a sixfold increase in cases during the past 30 years, according to the National Cancer Institute. Understanding how and why the cells change in some cases and not others has been a major challenge for investigators.

Researchers compared telomere length and telomerase activity in biopsy specimens from 38 patients with gastroesophageal reflux disease (GERD) and from 16 control patients. This new line of research suggests that the continuous acid bath affecting the esophageal cells causes them to divide more frequently in order to regenerate the damaged lining. However, each time the cells divide, the telomeres at the end of DNA become shorter. When they become too short, the aging cell can no longer divide.

Scientists suspect that when cells can no longer divide, other cells might infiltrate the area to make up for the loss. Those cells may be more likely to generate the acid resistance that makes them more likely to turn cancerous.

"If the telomerases get short enough, maybe the cells can’t regenerate any more and maybe that’s why you start to see this change," said Dr. Spechler. "Perhaps the esophagus can't regenerate the normal skin-like squamous cells, and instead, it has to recruit cells from somewhere else, and that’s why you start getting these changes to intestinal-like cells."

Other studies by these university specialists suggest that the alternate cells that eventually take over might be bone marrow cells.

"There could be cells circulating from the bone marrow that wouldn't ordinarily end up in the esophagus. But if you shorten the telomeres enough and the esophagus can't regenerate anymore, perhaps these bone-marrow cells might have to replace that tissue, and bone-marrow cells can turn into intestinal tissue," Dr. Spechler said.

"This hasn't been proven, but we have some data that support that."

Drs. Souza, Spechler, and colleagues noted that bone marrow cells come into play to regenerate the esophageal lining in rats that have severe reflux.

"So the first paper shows that the telomeres are short, suggesting that the normal squamous cells might not be able to divide anymore, so they die out," Dr. Spechler said. "The second paper suggests that the bone-marrow cells may then come and take their place, giving rise to the intestinal cells instead of the normal, skin-like cells."

Further research will be needed to confirm that hypothesis, Dr. Souza said.

"It's an interesting series of experiments," she said. If confirmed, the research might also help scientists find a way to prevent bone marrow cells from invading or to identify markers that would allow an earlier diagnosis for Barrett’s esophagus, which is usually asymptomatic.

Hormonal Disorder Linked to Excessive Insulin

Elevated levels of insulin could be an early sign that girls whose mothers have polycystic ovary syndrome (PCOS) may also be susceptible to the disease, according to gynecologists who have found evidence of insulin resistance in young children. The findings could help determine whether daughters of women with PCOS are at a higher risk for PCOS.

PCOS is a common hormonal disorder that affects women of reproductive age. It can sometimes cause an inability to become pregnant. Symptoms include hairiness (hirsutism) resulting from excessive amounts of male hormones; irregular menstrual periods; and insulin resistance.

"We found insulin resistance in children who had entered puberty and whose mothers had PCOS," said Richard S. Legro, M.D., Professor of Obstetrics and Gynecology at Penn State's College of Medicine. "We did not find it in the youngest children, which suggests that the disease is triggered by puberty."

Dr. Legro and his colleagues sought to learn whether metabolic and reproductive abnormalities associated with the inheritable disease were more likely to show up in children whose mothers had PCOS and how parents could learn whether their child was at risk. The researchers designed a study to compare 38 boys and girls ages 4 to 14, whose mothers had PCOS, with 32 children in a control group.

They specifically looked for the early onset of androgen production (male hormones) and production of excess insulin.

"We collected samples of saliva and urine to analyze levels of insulin and sex steroids, respectively," explained Dr. Legro. "But we also looked for gonadotropins, hormones that stimulate sex steroids and provide the earliest sign of puberty."

The test indicated that older girls, but not boys, of PCOS mothers had significantly higher concentrations of salivary insulin. Compared with the controls, the girls also had lower levels of urinary hormones. According to Dr. Legro, the key finding of the study is that insulin levels appear to be elevated in daughters of PCOS mothers, which becomes more pronounced as they pass through puberty. Since the androgen levels were comparatively normal throughout puberty, and insulin resistance was found only in girls who had undergone puberty, Dr. Legro argues that insulin is the primary problem, whereas male hormones are a secondary problem.

Insulin is the real culprit in terms of stimulating the ovary, more so than gonadotropins. "You could say some of PCOS mothers build up excessive insulin during puberty, which in turn contributes to reproductive abnormality," explained Dr. Legro.

However, he cautioned that it might be too early to conclude that excessive insulin is the sole factor that makes daughters of PCOS mothers susceptible to the disease. He is also not sure whether hyperandrogenism—excessive male hormone levels—precedes or follows excessive levels of insulin.

Researchers say future longitudinal studies will focus only on girls to try to determine whether an abnormal level of insulin is the sole factor that causes reproductive abnormalities.

"That is the tantalizing question," the Penn State medical researcher said. "The ultimate goal would be to find the earliest sign that makes a child more susceptible to develop PCOS. Right now the earliest sign would be an elevation in insulin levels."

(Source: Journal of Clinical Endocrinology and Metabolism, 2008; 93:1576-1578.)