Canary in the Coal Mine: Calcium, Hyperparathyroidism, and Cardiovascular Disease

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If there's one thing that Houston Methodist endocrinologist Laila Tabatabai, M.D., would like to tell her cardiology and primary care colleagues, it's to pay attention to high calcium. Slight elevations in serum calcium may seem innocuous at first, but for Tabatabai, any persistent elevation in serum calcium "is a definite red flag that something is wrong." Levels even a few tenths of a point above normal (normal range usually 8.9-10.3 mg/dL, according to most labs), could be the first sign of hyperparathyroidism, which could have serious impacts on cardiovascular health and mortality.

The parathyroid glands, which are tucked behind the thyroid, regulate calcium homeostasis by controlled secretion of parathyroid hormone (PTH). When too much parathyroid hormone is released—as in hyperparathyroidism—a cascade of complex chemical interactions and feedback loops is disrupted. For the cardiovascular system, this may end in hypertension, heart failure, cardiac and vascular remodeling, and hypertrophy.

As Tabatabai and co-authors Spandana Brown, M.D., and Mary Ruppe, M.D., point out in a recent review article on the parathyroid and the heart, multiple studies have identified an association between hyperparathyroidism and cardiovascular mortality.[1] For instance, patients with primary hyperparathyroidism were more likely to die from cardiovascular events such as heart attack and stroke.[2] In a large multiethnic cohort study, patients with PTH levels ≥ 65 pg/mL (characteristic of hyperparathyroidism) were 50% more likely to have heart failure than those with levels under 65 pg/mL.[3]

Since non-endocrinologists are unlikely to routinely monitor PTH levels, routine calcium tests can act as the canary in the coal mine. Unfortunately, hyperparathyroidism and its link to cardiovascular disease is not widely recognized—the research is fairly recent—so red flags like calcium abnormalities are often overlooked, especially when patients are asymptomatic.

nutrient stores in response to a successful hunt/forage/trip to McDonald's. When we go to sleep, the heart's maintenance crew takes over to replace old or damaged proteins and lipids; this process is powered by energy reserves now free from the day's higher contractile demands.

"Many times, the patient is the one who's concerned about the laboratory abnormality," Tabatabai says. "I'll see patients in the clinic who say, 'My calcium's been elevated for years, and

CALCIUM CONFUSION

Serum calcium is a point of confusion for many patients who think of calcium in terms of dietary intake. However, serum calcium measures the calcium released from bone minus calcium excreted by the kidneys, all of which is regulated by PTH. The calcium absorbed from food through the small intestine has very little impact on serum calcium levels.[4] Nevertheless, the misconception can lead patients take logical, but ultimately harmful, action. Tabatabai explains:

"Many patients will look at the elevated calcium which occurs from hyperparathyoidisim and think that completely stopping all calcium and quitting all dairy products will help. I tell patients that's the exact wrong thing to do. That strategy tends to backfire because the body is very sensitive in terms of recognizing how much calcium is coming in, and if your body senses a calcium deficiency, it will stimulate even more PTH production.

However, there is some evidence that taking calcium supplements can possibly lead to coronary calcification or calcification of the renal tubules. This is a pretty controversial area that we don't fully understand. But what I always end up telling my patients is that if they're able to get calcium from dietary sources—such as milk, cheese, yogurt, calcium-fortified orange juice, soy or almond milk, or dark, leafy greens—those options are always healthier and more natural than taking calcium tablets. If they consume 2-3 servings of low-fat or fat-free dairy products, they're able to get what they need over the course of the day without having to use calcium supplements.

Ultimately, you will never be able to cure hyperparathyroidism by stopping all calcium products. This is a condition in which the parathyroid glands are hyperactive, and stopping calcium will only make that worse."

my primary care doc told me that it was fine because I felt fine. I always worried because it showed up as bold and red and abnormal on my lab reports, but nothing ever got done.'" With all the other conditions treated by primary care physicians, Tabatabai notes, it's little wonder that "an elevation in calcium is not at the top of their list, but I do recommend referring those patients to an endocrinologist because elevated calcium could be an indication of many conditions, including hyperparathyroidism or malignancy. It's important that we don't sweep that lab under the rug."

High calcium may be a sign of primary hyperparathyroidism, the kind that spontaneously arises independent of pre-existing conditions. Tabatabai describes it as "parathyroid glands going rogue." The hyperactive gland(s)—usually one, but sometimes multiple —release too much PTH, causing calcium levels to rise. The hyperactive gland could be a parathyroid adenoma or multigland hyperplasia.

Secondary hyperparathyroidism is a much different phenomenon. As the name suggests, it is caused by another condition, usually as a result of vitamin D deficiency or chronic kidney disease. Laboratory diagnosis of secondary hyperparathyroidism is more complicated than that of primary hyperparathyroidism. For instance, with chronic kidney disease, PTH levels can safely be twice as high as normal through an adaptive response. Also, Tabatabai points out, secondary hyperparathyroidism may be associated with low serum calcium—at least at first. If secondary hyperthyroidism is not controlled, it can spiral into tertiary hyperparathyroidism, wherein PTH and calcium levels skyrocket. As the condition worsens, the cardiovascular damage accelerates—tertiary hyperparathyroidism happens most often in patients with end-stage renal disease on dialysis.

Although an endocrinologist is best equipped to diagnose hyperparathyroidism, Tabatabai says that her primary care and cardiology colleagues can help by following up on any calcium abnormality, high or low. She encourages physicians to check albumin, 25-hydroxyvitamin D, and PTH levels. "I don't expect non-endocrinologists to do a huge amount of workup," she says. "But it is very helpful for to have those laboratory studies up front. That way, we can often very quickly see what's going on with the patient."

Research suggests that early diagnosis is key since many of the cardiovascular complications may be at least somewhat reversible if treated early enough. Moreover, Tabatabai cautions, "if we don't treat the underlying parathyroid condition, the resulting cardiovascular insult is almost guaranteed to recur. Unfortunately, that's what we see in a lot of patients who have parathyroid disease that's not recognized or not treated until very late in life."

However, simply treating the hyperparathyroidism—by surgically removing the hyperactive gland(s) in primary hyperparathyroidism, or through vitamin D supplementation or kidney disease treatment in secondary hyperparathyroidism—may not be enough to solve the entire problem.

"Many of these issues, such as myocyte remodeling or changes in the vasculature that lead to hypertension or heart failure, took many years to take place. So the improvements that we see are also quite gradual," Tabatabai says. "The endocrine intervention helps these patients. However, I think cardiologists would definitely agree that these cardiac issues are so multifactorial that eliminating one problem (such as hyperparathyroidism) is very helpful, but it's probably not going to be the entire solution."

Fortunately, in addition cardiovascular advantages, there are other health benefits to be gained from treating primary hyperparathyroidism. Prompt intervention can avoid the side effects of uncontrolled primary hyperparathyroidism, such as kidney stones, bone loss, and osteoporosis.

From diagnosis through treatment, addressing the complex interplay between hyperparathyroidism and cardiovascular disease is a multidisciplinary effort. Achieving optimal patient outcomes often requires teamwork between endocrinologists, cardiologists, primary care providers, and surgeons—all beginning with that first irregularity in serum calcium.

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