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Hypertension's Lead Connection

Does low-level exposure to lead cause high blood pressure?

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"Paying for the sins of the past." That's how researcher Howard Hu describes a proposed disease process in which lead stored for decades in the skeleton puts people at risk of high blood pressure.

Previous research has linked this silvery white, poisonous metal to a host of ill effects in children, including learning disabilities, behavior problems, and brain damage. Now, Hu's study indicates that past exposures may be causing today's high blood pressure. If he's right, the public health impact would be significant.

"Tens of millions of Americans have been exposed over the years to lead," says Philip J. Landrigan of Mount Sinai Medical Center in New York. "Adults today grew up at a time when we were still putting several hundred thousand tons of lead into gasoline each year."

Indeed, the men who developed high blood pressure during the recent study had in their bones lead concentrations, or lead burdens, that came from decades of everyday exposures. Such exposures resulted principally from breathing in fumes from leaded gasoline, drinking tap water from lead pipes or pipes soldered with lead, and inhaling or ingesting lead-laced paint dust or chips.

Almost 50 million people in the United States suffer from hypertension. About 95 percent of them have what's known as essential hypertension, or artery-damaging high pressures of unknown origin. People with essential hypertension must take powerful antihypertensive drugs for the rest of their lives. If lead is responsible for this dangerous rise in blood pressure, researchers may be able to devise a therapy to fix the underlying problem, Hu speculates.

The lead-hypertension study, published in the April 17 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA), has received kudos, with the usual reservations, from other scientists. "This is very credible work...an elegant study," Landrigan says. "Like any study with major implications, it's got to be confirmed," he adds.

Epidemiologist Peter A. Briss at the Centers for Disease Control and Prevention in Atlanta calls the new study's findings important. "This gives us another piece in the puzzle linking lead exposure to high blood pressure in adults," Briss says.

Five years ago, Hu, an epidemiologist at the Harvard School of Public Health in Boston, and his colleagues set out to resolve a puzzling discrepancy. They knew that some earlier studies had demonstrated a positive association between hypertension and the concentration of lead circulating in the bloodstream. Other studies had discovered no link between the two.

Hu's team wondered if researchers had been looking in the wrong place for a connection. Concentrations of lead in the blood represent exposure to the metal within the last few months. Yet hypertension takes decades to develop. Hu decided to take a different tack, using a new technique that measures lead stored in the bones.

Following a person's exposure to lead, the kidneys excrete most of the metal. However, 7 to 10 percent of the remaining lead circulating in the bloodstream is later stored in the bones. Because the metal can stay there for a lifetime, researchers use it as a measure of cumulative lead exposure. For that reason, Hu and his colleagues thought that readings of lead in bone might prove a better predictor of hypertension than lead in the bloodstream.

The Harvard team relied on an instrument that looks like a dental X-ray machine and uses a technology called K X-ray fluorescence (KXRF) to measure the signals from lead and calcium in

the bone. “The ratio of those two signals is a very accurate measure of concentration of lead in bone mineral,” Hu says.

The researchers recruited men who were already participating in the Normative Aging Study, established by the Department of Veterans Affairs in 1961 to observe almost 2,300 men for 30 years. The men, mostly white veterans from the Boston metropolitan area, underwent a thorough examination before being enrolled in the study. Those who suffered from hypertension or other chronic health problems were excluded.

Hu’s team focused on 590 men who were seen at a research clinic at the Brigham and Women’s Hospital in Boston between August 1991 and December 1994. During that time, the researchers noted participants who had started taking antihypertensive medication or developed high blood pressure. They defined hypertension as systolic (heart-contracted) blood pressure higher than 160 millimeters of mercury or diastolic (heart-resting) pressure of 96 or higher.

High blood pressure forces the heart to work harder. Over time, high blood pressure can lead to heart attacks and strokes.

Using KXRF, the researchers measured the lead stored in two bones, the patella (kneecap) and the tibia (shin bone).

They found that lead in the tibia of the participants ranged from less than 1 to 96 micrograms per gram of bone mineral; lead in the patella ranged from 1 to 142 micrograms per gram. Both measures rose with age in a linear fashion. They also represent fairly low exposures to lead and are typical for middle-aged white men in the United States, Hu says.

When the researchers did a statistical analysis, they found that men with hypertension typically had higher lead values in these bones than nonhypertensive men. After controlling for other factors that cause hypertension, the researchers found that lead stored in the tibia, but not in the patella, appeared to predict high blood pressure. They speculate that lead in the tibia is socked away for a lifetime, whereas lead in the patella often leaches out into the bloodstream. The long-term accumulation of lead may put people at risk of hypertension, they suggest.

Indeed, the analysis demonstrated that men with 37 micrograms of lead per gram of bone mineral in the tibia (the 90th percentile of this group) ran a 50 percent greater risk of hypertension than men with 8 micrograms of lead (the 10th percentile).

If lead and high blood pressure are linked, as Hu’s study suggests, does it follow that when lead sequestered in the bone leaches out, it increases blood pressure directly? Hu believes that lead in bone may be a marker for long-lasting, but low, concentrations of lead in the blood.

A second study hints at how lead might cause high blood pressure.

Led by Rokho Kim, also at the Harvard School of Public Health, it generated data suggesting that even low exposures to lead may harm the kidneys. That subtle injury, in turn, leads to a rise in blood pressure, Kim and his colleagues speculate in the same issue of JAMA.

Originally, however, Kim’s group knew only that at very high doses, such as those incurred by workers in an occupational setting, lead damages the kidneys. No one was certain whether lead in low doses would also be a problem.

So Kim and his colleagues, including Hu, again turned to the Normative Aging Study for participants. They settled on 459 men who had not taken part in the hypertension study and who had no evidence of kidney damage at the study’s start in 1961.

The researchers had access to 15-year-old frozen blood samples for each man. They also had data on a test that measures concentrations of creatinine in the blood. People with kidney damage have higher than normal amounts of this compound in their bloodstream. With such information, the researchers believed they could reconstruct a picture of lead exposure and kidney function for each participant during a 15-year period.

Kim and his group controlled for age, smoking, alcohol consumption, education, and body

mass index, all factors that relate to hypertension and could confuse the analysis. They found that lead concentration in the blood was positively and significantly associated with the concentration of creatinine in the bloodstream. Indeed, their analysis demonstrated that a 10-fold rise in lead concentration had the same impact on kidney function as 20 years of aging.

Their research revealed that increased lead in the bloodstream precedes a decline in kidney function. This observation is very important because the link between lead and kidney dysfunction would be meaningless if the kidneys started to malfunction first. In that case, one would expect more lead to slip past the kidneys and into the bloodstream, Kim says.

Usually, the malfunction observed in the study was slight. "It is a very small impact on renal function" that would probably go unnoticed by most individuals, Kim says.

"We're not talking about an effect that will thrust you into the health care system," Hu says. "But if you had borderline function to begin with, it could push you over the edge into clinical kidney failure." He points out that renal disease is silent, rarely showing any symptoms until the kidneys stop working altogether.

Kim and his colleagues believe that lead damages the kidneys directly. Previous research suggested that lead may injure the renal tubule cells.

The kidneys help regulate blood pressure, Hu points out. If low concentrations of lead do harm them, even minimally, one could expect an impact on blood pressure. Diseases known to cause major damage to the kidneys, such as polycystic kidney disease, result in a deadly rise in blood pressure, Hu adds.

Hu says his data suggest that 16 percent of men age 50 and over who suffer from hypertension can attribute their illness, at least in part, to lead. However, the lead, kidney, and hypertension connection could also affect middle-aged women and others not included in this initial study.

Indeed, Hu worries that lead's impact might prove more destructive for women. They are more susceptible to the bone-wasting disease osteoporosis, he notes. "If the release of lead from bone plays an active role in the blood pressure process, then women might experience a heightened effect of lead on blood pressure," Hu says.

Hu notes that black people in the United States run a higher risk of hypertension than their white counterparts. They are also disproportionately exposed to lead in a deteriorating urban environment. "If you put the two facts together, it really makes you wonder whether lead might be responsible for the higher rate of hypertension [in the black population]," Hu says.

The average age of recruits in the lead study was 66, but the researchers suspect the lead and hypertension connection probably affects younger people as well.

"The fact of the matter is that for many, many decades the environment in this country was significantly lead contaminated," says Ellen Silbergeld, an environmental toxicologist at the University of Maryland at Baltimore. From the 1940s through the 1970s, cars spewed out exhaust that contained lead. During that time, houses were built with lead water pipes, a practice that contaminated public water supplies, she notes.

Although the United States has taken steps to reduce lead in the environment, Kim and Hu believe more should be done. They would like to see a tightening of the federal regulations for exposures to lead in the workplace. Current regulations allow concentrations of 40 micrograms of lead per deciliter of blood. "Very few of these subjects in our study had blood lead levels over 40 at any time," Hu says. Yet such low values may, as time goes on, cause renal damage and high blood pressure, he says.

For researchers, the findings bring up some tantalizing leads. If lead is damaging the kidneys and thus causing high blood pressure, is the injury reversible? If scientists can figure out how to repair that damage, millions of people who now take drugs to control their high blood pressure might get a cure instead of maintenance treatment, Hu says.

Would a drug that reduces the body's burden of lead bring down soaring blood pressures? Hu and his colleagues plan to test that hypothesis in a clinical trial of men with high lead burdens and hypertension that is difficult to control with medication.

For the millions of people with high blood pressure, such questions are far from rhetorical. □