Does a Lack of Calcium Cause Hypertension?

Several recent studies link calcium and high blood pressure but the medical community is divided on how to interpret them

When David McCarron of the Oregon Health Sciences University recently suggested that a lack of calcium—and not an excess of sodium in the diet—is associated with high blood pressure, he provoked strong reactions, both of support and of criticism. "McCarron's hypothesis is nonsense," says Mordecai Blaustein, a physiologist at the University of Maryland Medical School. On the other hand, John Laragh, director of the Cardiovascular Center at Cornell University Medical Center, has data that are consistent with what McCarron reported in a recent article in *Science*.*

McCarron makes use of a national survey to ask whether the diets of people with hypertension differ at all from those of people with normal blood pressure and, if so, how. He found that hypertensives consume, if anything, less sodium than those with normal blood pressure and significantly less calcium, potassium, vitamin A, and vitamin C. The meaning of these findings is not yet clear, but the calcium finding in particular may be an important clue to the regulation of blood pressure. This finding recently has been replicated by several other investigators.

The idea that a lack of calcium, rather than a surfeit of sodium, may cause high blood pressure has, predictably, raised some researchers' ire. Blaustein, for example, remarks, "Most who study calcium levels don't believe those data." Blaustein and others question first of all the reliability of dietary recall surveys. Then they ask what sort of physiological mechanism could possibly account for such calcium effects.

If there is a relationship between calcium and high blood pressure, it does not seem to be a simple one. Calcium infusions can raise blood pressure in both humans and laboratory animals. So can severe calcium deficiencies. There does not appear to be a consistent relationship between the amount of calcium in the serum and blood pressure. And, as McCarron himself stresses, calcium almost certainly interacts with other ions, such as sodium and potassium, to produce its effects.

McCarron has been curious about the possible connection between calcium and high blood pressure for some time. He was surprised to find virtually nothing in the literature on the topic so, a few years ago, he decided to do a "small but careful pilot study" on newly diagnosed hypertensives.

With the help of a nurse practitioner, he characterized 34 newly diagnosed hypertensives and 34 people with normal blood pressure. The hypertensives, he found, had biochemical markers related to calcium metabolism. Their parathyroid hormone concentrations were moderately elevated, they excreted too much calcium, they had too little phosphorus in their serum, and they excreted too much cyclic AMP. "As a group, they were struggling to stay in calcium balance," McCarron concludes.

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The next step for McCarron was to look at animal models of hypertension. He and his colleagues, studying the spontaneously hypertensive rat, saw the same biochemical defects they observed in the patients in the pilot study. Moreover, McCarron found, the rats were "exquisitely sensitive to calcium. If we added calcium to their diet, their blood pressure would decrease significantly and in some cases virtually normalize."

A second search of the literature for epidemiological data on calcium and hypertension was undertaken. Once again, virtually nothing. One clue, however, was a sentence in a paper by Herbert Langford of the University of Mississippi saying that blacks in Mississippi with hypertension consume less calcium.

"I went out and hired a nutritionist," McCarron recalls. 'We were going to find out if there is a difference [in calcium consumption by hypertensives].'' When he completed his study of 46 people with high blood pressure and 44 with normal blood pressure, he found that the hypertensives consumed about 22 percent less calcium.

"We started looking for a very large data base," McCarron says, to see if the calcium results held up across the entire U.S. population. Fortunately, such a data base was available from the National Center for Health Statistics. Called Health and Nutrition Examination Survey I (HANES I), it is a sample designed to be representative of the entire U.S. population. The center surveyed 20,749 Americans between 1971 and 1975, asking them to recall what they had eaten in the past 24 hours and taking a medical history. In addition, the survey participants had their blood pressure measured. McCarron and his associates eliminated from the sample those persons who were taking medication to control their blood pressure, who were on special diets, such as low-salt diets, and who were pregnant. That left them with 10,372 subjects.

The most surprising and most controversial finding had to do with sodium rather than calcium. The hypertensive subjects consistently ate less sodium. But, as McCarron points out, the sodium findings were not statistically significant. Moreover, others who have analyzed the HANES I data, including William Harlan of the University of Michigan and Manning Feinleib, the director of the National Center for Health Statistics, did not see any relation at all between sodium consumption and blood pressure when he looked at the population as a whole. The difference between their results and McCarron's may be due to slightly different methods of statistical analysis or to different estimates of the amounts of sodium in various foods.

The strongest relationship between diet and blood pressure was with calcium consumption. Persons with hypertension consistently consumed significantly less calcium than persons with normal blood pressure. This finding was confirmed by Harlan and Feinleib in their independent analyses of the HANES I data and also by Harlan when he analyzed the more recent HANES II data which were collected between 1976 and 1980. The relationship is beginning to be reported in other large-scale studies.

McCarron and his associate Cynthia Morris and, independently, Lawrence

*D. A. McCarron, C. D. Morris, H. J. Henry, J. L. Stanton, *Science* **224**, 1392 (1984).

Resnick, John Nicholson, and Laragh at Cornell Medical Center now have evidence that calcium supplements can lower blood pressure, at least in some hypertensives. McCarron and Morris did a double-blind placebo-controlled crossover study of 48 hypertensives and 32 volunteers with normal blood pressure. The participants took 1000 milligrams of calcium a day for 8 weeks and a placebo for 8 weeks. Not everyone responded to the calcium, and more participants with hypertension responded than participants with normal blood pressure. Forty-four percent of the hypertensives in the study had a reduction in their blood pressure of more than 10 mmHg when they took the calcium supplements.

Laragh and his colleagues have biochemical evidence that one class of hypertensives—those with low levels of the kidney hormone renin—is likely to be helped by calcium supplements. These hypertensive patients, who constitute about one-third of all patients with high blood pressure, have abnormally low levels of calcium in their blood, tend to have mild hypertension, and have blood pressure that rises when they add salt to their diet. High-renin hypertensives, Laragh finds, do not respond to salt, often have severe hypertension, have too much calcium in their blood and, he predicted, will not be helped by calcium supplements.

When Nicholson, Resnick, and Laragh gave low-renin hypertensives 2000 milligrams of calcium a day, their blood pressure decreased significantly—some of these patients had blood pressure drops of 20 mmHg. The high-renin patients, on the other hand, had blood pressure increases of as much as 10 mmHg when they took the calcium supplements. Laragh speculates that the reason a lack of dietary calcium keeps appearing in population studies as a correlate of hypertension is that all of the study investigators focused on the diets of untreated hypertensives, which usually means people with mild hypertension and low renin levels.

Skeptics of McCarron's data suggest that dietary recall may not be completely reliable. Edward Freis of the Veterans Administration Medical Center in Washington, D.C., suspects that it may be even worse than most people realize for the study of diet and hypertension. Untreated hypertensives, Freis notes, have been shown in several studies to have memory defects. Thus, Freis proposes, the hypertensives in the HANES surveys may remember less of what they eat than the persons with normal blood pressure. McCarron rejects Freis' hypothesis, saying it would have to be an unusual memory defect to cause the hypertensives to particularly forget specific nutrients.

Another criticism of dietary recall to determine the precedents of high blood pressure is that hypertension is thought to be a chronic disease, one that may be caused by 10 or 20 years of dietary deficiencies, if diet has anything to do with it at all. So a study that asks about only the last 24 hours' food intake is, as Harlan puts it, "a pretty slender reed." Still, the recall studies are not the only evidence that calcium deficiencies may be involved in the genesis of hypertension and, as Laragh points out, the dietary recall studies are no worse than cross-cultural dietary comparisons that are cited so often in support of the hypothesis that excess sodium causes high blood pressure.

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But the mechanisms by which calcium may affect blood pressure are, if anything, even less clear than the mechanisms proposed to account for sodium's possible effects. Hypertension occurs when the microscopic arterioles, which feed blood into the capillaries, contract and stay contracted, generating an effect like tightening the nozzle of a hose. To understand high blood pressure, it is necessary to understand what controls the contraction of these blood vessels.

"There is no question that calcium is in the final pathway to the generation of high blood pressure," Blaustein remarks. "A rise of calcium inside the cell leads to an increased contraction of the artery smooth muscle. That observation several years ago led to calcium channel blockers for the treatment of hypertension. Anything you do to block calcium in the cell reduces blood pressure."

McCarron responds that when calcium is available to cells in adequate amounts it stabilizes the arterial membranes, blocks its own entry into the cells, and makes the arterial smooth muscles less likely to contract. As for calcium blockers, he says, "that is a purely semantic argument. Calcium blockers prevent calcium from entering the cell. Because calcium blockers can lower blood pressure, people make the leap that there is an advantage to restricting calcium. But if you reduce calcium, that opens the calcium channels of the cell even more." He notes that cells regulate their intracellular calcium so that if a cell has enough calcium, it inhibits the entry of any more and if it has too little its calcium channels let more in. "Calcium," he says, "has a dual effect depending on the amount in the tissues." Too much or too little calcium can raise the blood pressure. Moreover, he says, it may not be calcium alone but calcium in conjunction with other ions such as sodium and potassium that relax the arterioles.

But despite the abundance of provocative hypotheses, truth is that no one really can explain the calcium data. And, says Harlan, it may be too much to expect anyone to. "It is hard to take epidemiological data and come up with mechanisms. The data point the way to basic research."

Still, says McCarron, it is not too soon to make some simple dietary recommendations. He suggests that persons with hypertension eat balanced diets with sufficient dairy products or calcium supplements, if necessary to assure a calcium intake of 800 to 1000 milligrams a day, which is consistent with the National Academy of Sciences' recommendations. There is no reason for healthy individuals to restrict sodium and, in fact, the epidemiological data indicate that too little sodium may negate the beneficial effects of calcium, McCarron concludes. Others disagree.

William Friedewald, who is director of the division of epidemiology and clinical applications at the National Heart, Lung, and Blood Institute says that the data on calcium "are exciting and call for more research. But they are not *nearly* at the level to make dietary recommendations." So far, the NHLBI recommends only sodium restriction and weight reduction, if necessary, as nondrug methods of controlling blood pressure.

The American Heart Association adopts the same cautious position. In addition, its president, Antonio Gotto, points out that foods high in calcium also tend to be high in saturated fats. "The evolving concepts on calcium in the regulation of high blood pressure will be watched carefully and utilized appropriately as they reach maturity," Gotto states.—**GINA KOLATA**

Additional Reading

1. M. R. Garcia-Palmieri *et al.*, *Hypertension* **6** (No. 3), 322 (1984).
2. W. Harlan, *Am. J. Epidemiol.* **120** (No. 1), 17 (1984).
3. L. M. Resnick *et al.*, *N. Engl. J. Med.* **309**, 888 (1983).