ALTERNATIVE MEDICINE
AN EVIDENCE-BASED APPROACH

Pomegranate for Cardiovascular Disease

History of Use

In Greek mythology, Persephone was the daughter of Zeus, king of the gods, and Demeter, the goddess of agriculture. Persephone was pursued and abducted by Hades, the god of the underworld, and Demeter retaliated for the loss of her daughter by ruining the harvest and causing starvation. Zeus finally convinced Hades to give up the girl—but this would be possible only if she had eaten nothing in the underworld. Unfortunately, she had eaten four pomegranate seeds, so a compromise was reached: Persephone would spend part of the year on earth—the months that corresponded to the growing season—and would spend the remaining months in the underworld with Hades.

► Pomegranate fruit has a long history of use in the folk medicine of many cultures.
► Small clinical studies suggest possible benefits of pomegranate juice in atherosclerosis and coronary artery disease.

Many religions have ascribed significance to the fruit of *Punica granatum*. In Judaism, the pomegranate is said to contain 613 seeds, one for each of the commandments in the Torah. The pillars of King Solomon's temple and the robes of kings were adorned with depictions of pomegranates. In Buddhism, the pomegranate, the citrus, and the peach are considered the three blessed fruits.

In Christianity, the fruit is a symbol of resurrection and is often included in depictions of Christ and his mother. In the Koran, paradise is described as having gardens in which pomegranate trees are found, and, according to Islamic legend, each earthly pomegranate fruit contains one seed from paradise (BMJ 2000;321:1153-4).

Rationale for Use

Like other berries and grapes, pomegranates possess significant antioxidant properties deriving from components such as polyphenolics, tannins, and anthocyanins. Animal studies have suggested that dietary supplementation with these plant antioxidants inhibits events associated with atherosclerosis, including LDL oxidation and macrophage foam cell formation.

Clinical Investigations

A group of researchers from the Lipid Research Laboratory, Rappaport Family Institute for Research in the Medical Sciences, Rambam Medical Center, Haifa, Israel, have been investigating the effects of pomegranate juice on various aspects of cardiovascular disease.

In their early studies, they observed that pomegranate juice consumption reduced oxidative stress, atherogenic modifications to LDL, and platelet aggregation in mice and humans (Am. J. Clin. Nutr. 2000;71:1062-76). It also inhibited serum angiotensin-converting enzyme activity and lowered systolic blood pressure in a small group of hypertensive patients (Atherosclerosis 2001;158:195-8).

They then investigated the effects of pomegranate juice on various clinical parameters in patients with carotid artery stenosis. A group of 19 patients ranging in age from 65 to 75 years with asymptomatic, severe carotid artery stenosis were randomized to receive 50 mL of pomegranate juice or placebo each day for 1 year.

At baseline, B-mode ultrasound images of carotid artery wall boundaries were obtained, and intimal medial thickness (IMT) was measured at the far wall of the distal common carotid arteries. Atherosclerotic plaques were imaged and their length and width assessed, and flow velocities in the internal carotid arteries were calculated at sites of stenosis.

Among the 10 patients who consumed pomegranate juice, the mean IMT of the left and right common carotid arteries decreased by 13%, 22%, 26%, and 35% at months 3, 6, 9, and 12, respectively. In the placebo group, mean IMT increased significantly, by 9%, from 1.52 mm to 1.65 mm (Clin. Nutr. 2004;23:423-33). Average IMT in middle-aged men ranges from 0.7 mm to 1.2 mm.

Mean systolic blood pressure fell from 174 mm Hg at baseline to 153 mm Hg at 12 months, and mean peak systolic velocity in both left and right carotid arteries fell by 21% in the pomegranate juice group.

In the pomegranate group, serum oxidative state—evaluated by measurement of the level of antibodies against oxidized LDL—fell by a significant 24% in the first month and by an additional 19% by the third month.

Serum glucose and lipid concentrations were not significantly altered, but the lipid peroxide content in the atherosclerotic lesions of patients in the pomegranate group was significantly reduced, by 61% and 44% at 3 and 12 months, respectively.

The authors noted that, "in addition to the regression of the carotid lesion size, the lesion itself may be considered less atherogenic after pomegranate juice consumption, as its cholesterol and oxidized lipid content decreased, and since its ability to oxidize LDL was significantly reduced."

A group of California researchers including Dr. Dean Ornish also has been evaluating pomegranate juice in 45 patients with coronary heart disease and myocardial ischemia. Patients were randomized to receive 240 mL/day of pomegranate juice or a sports drink of similar caloric content, taste, and appearance. They were evaluated by single-photon emission computed tomographic scintigraphy at rest and during treadmill or pharmacologic stress testing at baseline and at 3 months, and the degree of inducible ischemia was calculated.

Myocardial perfusion improved by an average of 17% in the pomegranate group after 3 months, and worsened by an average of 18% in the control group, for a relative between-group difference of 35% (Am. J. Cardiol. 2005; 96:810-4). Angina episodes decreased by 50% in the treatment group and increased by 38% in the control group. The benefits were seen without any change in cardiac medications.

The investigators acknowledged that their sample size was small, but said that the clinically and statistically significant improvements seen "suggest that daily consumption of pomegranate juice may have important clinical benefits in this population." Both groups of researchers recommended that larger, long-term studies be conducted to establish a possible clinical role for pomegranate juice in patients with cardiovascular disease.

—Nancy Walsh

Obesity Protective in Acute and Chronic HF

BY BRUCE JANCIN
Denver Bureau

DALLAS — The obesity paradox previously described in patients with chronic systolic heart failure has, for the first time, been shown to be strikingly evident in acute heart failure as well, Dr. Gregg C. Fonarow reported at the annual scientific sessions of the American Heart Association.

An analysis of 108,927 hospitalizations recorded in the Acute Decompensated Heart Failure Registry (ADHERE) showed that in-hospital mortality decreased in near-linear fashion with increasing body mass index (BMI) quartile. (See box.)

The same marked reduction in in-hospital mortality seen in heavier ADHERE participants who had reduced systolic function was also seen in those with preserved systolic function, added Dr. Fonarow, professor of medicine at the University of California, Los Angeles, and director of the Ahmanson-UCLA Cardiomyopathy Center.

The paradox lies in the fact that obesity is a well-recognized independent cardiovascular risk factor in the general population, yet in chronic or acute heart failure, it is somehow protective.

The bottom line is that the paradox in acute heart failure is a real phenomenon. "Given the huge number of hospital episodes we're looking at here, the results are irrefutable," Dr. Fonarow said.

The obesity paradox has potentially enormous implications for managing acute decompensated heart failure, which is the primary or secondary diagnosis in 3 million U.S. hospitalizations annually. The next step in the research is to give acute nutritional support when normal-weight or underweight patients—those with, say, a BMI below 27 kg/m^2—present at the hospital in acute heart failure, and then to study whether their short-term mortality is thereby lowered.

"The broad implication is that this represents half of all acute heart failure hospitalizations," Dr. Fonarow said in an interview.

"We're seriously thinking of doing pilot studies looking at whether we can improve measures of cardiac function and nutritional status in these patients through acute nutritional support—and if that looks promising, to go forward with an interventional trial," he said.

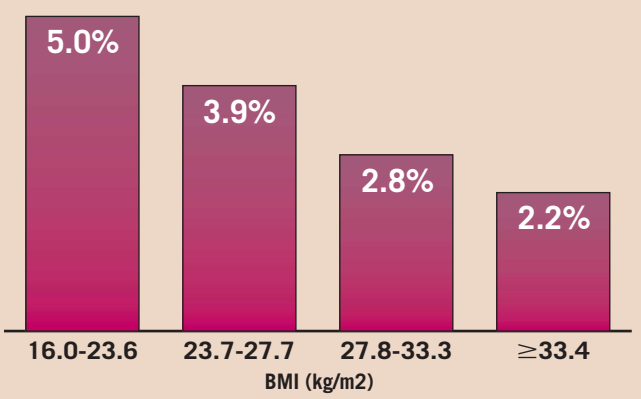
Only through such studies will physicians learn whether obesity is causative of reduced mortality in acute heart failure patients or whether it is merely a marker for lower risk. It is worth noting, though, that even after adjustment for known predictors of in-hospital mortality in acute heart failure—including age, gender, blood urea nitrogen, creatinine, blood pressure, and dyspnea at rest—patients in the lowest BMI quartile had a highly significant 46% greater in-hospital mortality than did those in the top quartile, who had a BMI of at least 33.4.

The same held true when patients were grouped by World Health Organization BMI category rather than by quartile. Patients with a BMI less than 18.5 had an in-hospital mortality of 6.3%. The rate was 4.6% in normal-weight patients (BMI 18.5-24.9), 3.4% in overweight patients (BMI 25.0-29.9), and 2.4% in obese patients.

The obesity paradox cannot be explained merely as a reflection of cachectic patients being unable to handle the stress of acute illness. After all, in-hospital mortality was increased even in normal-weight patients, compared with those who were overweight or obese, Dr. Fonarow said.

ADHERE is funded by Scios Inc. ■

In-Hospital Mortality by BMI in ADHERE



Note: Based on data from 108,927 patients hospitalized with acute decompensated heart failure.
Source: Dr. Fonarow