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File: ■ Coffee (*Coffea arabica*, Rubiaceae)
■ Tea (*Camellia sinensis*, Theaceae)
■ Caffeine
■ Liver Disease

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RE: Coffee and Caffeine Intake Are Associated with Lower Risk for Advanced Hepatic Fibrosis in Patients with Hepatitis C

Khalaf N, White D, Kanwal F, et al. Coffee and caffeine are associated with decreased risk of advanced hepatic fibrosis among patients with hepatitis C. *Clin Gastroenterol Hepatol*. August 2015;13(8):1521-1531.e3.

One of the most popular beverages worldwide, the consumption of coffee (*Coffea arabica*, Rubiaceae) is associated with a number of health benefits, including protection against the development of liver injury (hepatoprotection). Also, there is an inverse association between coffee consumption and hepatocellular carcinoma with or without chronic hepatitis C virus (HCV) infection. These authors used data from a cross-sectional study among U.S. veterans with chronic HCV infection to investigate the association between caffeinated and decaffeinated coffee, tea (*Camellia sinensis*, Theaceae), and soda intake and the development of HCV-related advanced liver fibrosis. Their secondary objective was to determine the extent to which insulin resistance mediates the association between caffeine intake and the severity of liver fibrosis.

The study was conducted at the Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas. Participants were veterans aged 18 to 70 years with confirmed HCV viremia who were prospectively recruited from a dedicated HCV clinic at the medical center between January 5, 2009 and November 30, 2013. The participants were not receiving antiviral therapy at the time of recruitment.

At baseline and after 12 weeks, participants underwent fasting blood draws for clinical laboratory tests, had anthropometric measurements taken, and body mass index (BMI) scores calculated. They completed a detailed questionnaire about their lifetime use of alcohol, tobacco (*Nicotiana tabacum*, Solanaceae), injection drugs, marijuana (*Cannabis sativa*, Cannabaceae), and other recreational drugs, as well as the presence of comorbid conditions, such as diabetes mellitus. All participants were scored using the Model for End-Stage Liver Disease (MELD) instrument, which assesses the severity of chronic liver disease.

The participants also provided information on their intake of caffeinated and decaffeinated coffee, tea, and carbonated soda, and their use of creamers and sweeteners. Cumulative lifetime exposure to coffee was determined by their reported daily intake in each decade of life starting with the 20s. For assessing average caffeine content, the authors estimated 137 mg for each 8 oz cup of coffee, 30 mg for each 8 oz cup of tea, 46 mg for each 12 oz can of caffeinated soda, and 0 mg for decaffeinated beverages.

The exposure variables were caffeinated and decaffeinated coffee intake, tea intake, and soda intake, and caffeine intake overall and from each beverage. The main outcome variable was advanced hepatic fibrosis as scored by using the FibroSURE test, which estimates the level of liver fibrosis and inflammation.

The study included 910 veterans with chronic HCV infection. Based on FibroSURE scores, 342 (37.6%) had advanced fibrosis (AF); the remaining 568 (62.4%) with mild fibrosis served as controls for the analysis. Most of the participants were male (98%), African-American, and chronic alcohol users. Those with AF were older (average, +1.8 years), had a higher BMI, and were more likely to have type 2 diabetes mellitus, metabolic syndrome, and higher MELD scores than the controls. Among nondiabetic participants, AF cases were more likely than controls to be insulin resistant based on a baseline fasting homeostasis model assessment-insulin resistance (HOMA-IR) score of ≥ 3. They were also more likely to have received prior HCV antiviral therapy. Though none were receiving treatment at the time of the study, all participants had detectable HCV RNA levels, confirming the presence of HCV in the blood.

In terms of liver inflammation, 252 participants (27.7%) were classified as advanced inflammatory activity cases and 658 (72.3%) were classified as mild inflammatory activity controls based on FibroSURE scores. There was no association between caffeine intake and severity of inflammation.

Most participants (54.6%) reported drinking some caffeinated coffee within the year before the study, with 47.2% drinking 1 or more cups daily. The controls had a higher average daily intake of caffeinated coffee compared with the AF cases (P=0.038) and more controls than AF cases reported drinking an average of 1 or more cups daily (P=0.045).

About 70% of participants reported drinking caffeinated tea within the preceding year; 22.7% consumed 1 or more cups daily. Tea intake, both caffeinated and decaffeinated, was not significantly different between the AF cases and controls. However, among the 413 non-coffee drinkers, caffeinated tea use was more common among controls than among AF cases (P=0.03).

There was no association between any consumption of caffeinated or decaffeinated soda and AF. Although consuming ≥ 1 can of caffeinated soda daily was significantly associated with a decreased risk for hepatic fibrosis (P=0.015), this association was reduced after adjusting for age, BMI, and alcohol use, and for MELD score and the presence of metabolic syndrome (P=0.047). And it was further attenuated when adjusted for diabetes and HOMA-IR scores (P=0.063). In addition, among the subset of non-coffee drinkers, intake of ≥ 1 can of caffeinated soda was not significant.

Overall, average daily caffeine consumption from all beverages was higher in the controls (273.8 mg) than in the AF cases (218.2 mg) (P=0.013), as was the average daily intake of caffeine from coffee (P=0.028). Caffeine was consumed mostly from coffee, followed by soda and then tea. Stratified by dose, participants consuming ≥ 100 mg caffeine daily from any source had a significantly reduced risk of AF (P=0.014), as did those consuming ≥ 100 mg caffeine daily from coffee (P=0.035); however, the association was not significant among non-coffee drinkers consuming ≥ 100 mg caffeine daily. The average daily intake of coffee in prior life decades was not significant.

There were no significant associations between AF and the use of creamers/whiteners (37% of the participants) or sweeteners (23.8% of the participants).

Among the 650 nondiabetic participants, those with a HOMA-IR value < 3 (in the normal range) were significantly more likely to consume more than 100 mg of caffeine daily than were the participants with HOMA-IR values of ≥ 3 (P=0.012). This association between caffeine intake and decreased risk of insulin resistance was significant after adjusting for age, BMI, and alcohol use (P=0.022); MELD score (P=0.024); and the presence of metabolic syndrome (P=0.017).

An average daily intake of 100 mg or more of caffeine from all sources was associated with a significantly decreased risk for AF (P=0.02) after adjusting for age, alcohol use, and BMI, and after adjusting for MELD scores in a second multivariate model. In a third model, adjusting for insulin resistance minimally reduced the association; however, the association between caffeine intake and decreased risk for AF remained significant after adjusting for the presence of metabolic syndrome (P=0.014).

In this study, an average daily intake of ≥ 100 mg of caffeine was associated with a lower risk for advanced hepatic fibrosis in patients with chronic HCV infection. In non-coffee drinkers, daily caffeinated tea intake (but not caffeinated soda) was also associated with decreased risk of progressive liver disease. Overall, consuming caffeinated coffee or caffeinated tea is more beneficial for patients with HCV than consuming other caffeinated beverages or decaffeinated coffee.

"If validated in other HCV-infected populations in the United States, our results suggest that a relatively low (and therefore potentially more tolerable dose) of caffeine, particularly from caffeinated coffee and possibly from tea, may convey a substantial reduction in fibrosis progression." The authors conclude that "prospective studies are warranted to determine the optimal dose and preparation of caffeinated beverage intake that could be safely and tolerably recommended for prevention of progressive liver disease in HCV patients in routine clinical practice."

—Shari Henson

The American Botanical Council has chosen not to include the original article.