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Commentary

Coffee Consumption and Prevention of Cirrhosis: In Support of the Caffeine Hypothesis

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Coffee is acknowledged as the most widely used drug worldwide. Coffee is also a foodstuff, so its use is often used to satisfy dietary urges. When used as a drug, coffee is normally consumed as a stimulant rather than to treat or prevent particular diseases. Recently, coffee consumption has been inversely related to progression of liver fibrosis to cirrhosis and even hepatocellular carcinoma. Experiments in cellular and animal models have provided biological plausibility for coffee as an antifibrotic agent in the liver. A recent article examined one of the key questions regarding the antifibrotic role of coffee—specifically what is the primary antifibrotic agent in coffee? This article briefly reviews the relevant issues with regard to coffee as an antifibrotic agent for patients with chronic liver disease.

Key words: Coffee; Caffeine; Cirrhosis; Adenosine; Liver fibrosis

INTRODUCTION

It is acknowledged that coffee is the most widely used drug worldwide. While this is true, coffee is also a foodstuff with wide variation, so its use is often directed at satisfying dietary urges. When used as a drug, coffee is almost invariably used as a stimulant rather than to treat or prevent particular diseases. Thus, it has been an exciting revelation in recent years that coffee consumption is inversely related to progression of liver fibrosis to cirrhosis and even hepatocellular carcinoma (HCC).

As is often the case, epidemiological observations have preceded pathophysiological explanations for this effect. Only recently have experiments in cellular and animal models provided biological plausibility for coffee as an antifibrotic agent in the liver. In an important recent article, Arauz and colleagues[1] examined one of the key questions regarding the antifibrotic role of coffee—specifically what is the primary antifibrotic agent in coffee? Consideration of this question merits a brief review of the relevant issues with regard to coffee as an antifibrotic agent for patients with chronic liver disease.

DOES COFFEE REALLY PREVENT FIBROSIS, CIRRHOSIS, AND HEPATOCELLULAR CARCINOMA?

The vast majority of the data supporting the concept that coffee prevents unhealthful outcomes in patients with chronic disease comes from retrospective population-based studies. We recently reviewed the retrospective studies investigating associations between coffee consumption and changes in liver enzymes, liver fibrosis, and HCC in patients with a variety of chronic liver diseases[2]. Coffee consumption is inversely related with each of these outcomes, and there is a dose–response relationship. One important trial indicated that consumption of a single cup of coffee per day offered an odds ratio of 0.47, and four cups of coffee offered an odds ratio of 0.16 for risk of cirrhosis in patients with chronic liver disease (compared to coffee nonconsumers)[3]. These data have been confirmed in a recent prospective trial using noninvasive measurement of liver fibrosis in a healthy population, in which advanced liver fibrosis was inversely associated with coffee consumption, even when controlled for

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a variety of potentially relevant confounding variables[4]. Interestingly, this trial also showed an inverse association of herbal tea consumption with liver fibrosis, which merits further investigation but is outside the scope of this commentary.

WHAT IS COFFEE?

What is called and commonly recognized as coffee is actually a suspension of hundreds of compounds found in very low concentrations. The only two compounds found in coffee in large concentration are water, which is coffee's solvent, and caffeine. A serving of coffee is generally a true cup (8 oz), although servings have become larger in the late 20th century and early 21st century, making a 12-oz mug a common serving. This is important because the caffeine content in an 8-oz cup is approximately 90 mg, and the caffeine content in a 12-oz mug is closer to 135 mg. What all coffees have in common is that they are made from roasted coffee beans. However, the methods in which coffees are processed vary quite a bit. There are three methods used commonly: drip coffee, in which hot water is passed through ground coffee beans kept on a filter; boiling, in which ground coffee beans in hot water are brought to boil (the best example of this is Turkish coffee); and forced pressurization, in which hot water under increased pressure is forced through ground coffee (this is the method used in the preparation of espresso). This is relevant because the chemical composition of each of these varies—probably even more than variation caused by differences in the site of coffee bean harvest. In addition, caffeine content varies in each preparation.

IS SOME COFFEE ESPECIALLY EFFECTIVE AS AN ANTIFIBROTIC?

Interestingly, only drip coffee has been correlated with reduction in liver fibrosis, cirrhosis, and HCC. It has been a surprising but consistent observation that neither espresso (made from pressurized hot water) nor Turkish coffee (made from boiling coffee grounds without filtration) has been negatively correlated with fibrosis progression. The reasons for this are unclear but may be due to one of three possibilities. First, espresso and Turkish coffee are frequently drunk with refined sugar, which may offset the potentially beneficial effects of coffee, especially in fatty liver disease. Second, filtered coffee may remove substances that interfere with the compound(s) causing inhibition of liver disease progression. This is a plausible hypothesis because espresso and Turkish coffee contain more compounds and have different physical properties (the grounds present in Turkish coffee and the crema of espresso). Third, total caffeine consumption may be less in individuals drinking nondrip coffee. Although Turkish coffee and espresso have higher concentrations of caffeine than drip coffee, they are usually consumed in much smaller doses. For example, a single espresso (1.5 oz) usually contains 80 mg of caffeine compared to the 135 mg of caffeine found in a 12-oz drip coffee. However, these are open questions, and there is always a possibility that the primary studies that have examined this problem have been ineffectively designed or even underpowered to detect antifibrotic effects.

WHAT ARE THE MECHANISMS BY WHICH COFFEE EXERTS ANTIFIBROTIC EFFECTS?

Liver myofibroblasts, derived from hepatic stellate cells, portal fibroblasts, or possibly other sources, are the effector cells in liver fibrosis. It is likely that the sources of liver myofibroblasts vary by injury type; however, liver myofibroblasts share more common features than those that differ. In particular, liver myofibroblasts are the sources of collagen and other matrix components in liver fibrosis, and this provides the architectural distortion that is characteristic of cirrhosis and permissive for HCC[5].

Liver myofibroblasts express the A2a adenosine receptor, which is coupled to a variety of phenotypic changes that are profibrogenic. Most importantly, A2a activation links directly with matrix production. Caffeine is a pan-antagonist of adenosine receptors (including A2a), so there exists a strong possibility that caffeine is the active ingredient in coffee[6]. However, if this was the case, then two observations would be necessary. First, decaffeinated coffee should not block liver fibrosis (assuming that decaffeinated coffee is otherwise identical to caffeinated coffee, which is likely not to be true). Second, the effects of coffee should be able to be replicated by caffeine (assuming that the caffeine administered is bioavailable in roughly the same concentration as orally ingested coffee at the liver). The recent work by Arauz et al.[1] is one of the first to investigate this. Using common bile duct ligation, a model of biliary cirrhosis, the investigators showed that direct and indirect markers of liver fibrosis were blocked by caffeinated coffee or caffeine, but not by decaffeinated coffee. However, it is critical to note that the approximate dose of caffeine provided to experimental rats was 200 mg/day in rats of 400-g size (whether taking caffeinated coffee or caffeine). This would scale to approximately 15 g (15,000 mg) of caffeine, equivalent to a minimum of 100 cups of coffee per day in a 75-kg male human, so it is important to understand that the rats were "overdosed" if the scaling between rats and humans is linear. On another interesting note, liver enzymes were lowered even by decaffeinated coffee, so there is likely to be at least one other constituent of coffee relevant to liver fibrosis pathogenesis. The authors suggest that this may include antioxidant molecules, but there are insufficient studies to support this conclusively.

HOW SHOULD COFFEE BE PRESCRIBED?

As noted above, the strongest inverse association between coffee consumption and progression of liver fibrosis in patients with chronic disease occurs when individuals drink two to four cups of drip coffee per day. Despite biologic plausibility for nondrip coffee and other caffeine-containing beverages, there are no sufficient epidemiological data to support their use at this time. There is also insufficient evidence to suggest that more than four cups of coffee per day is of further therapeutic use.

Thus, I propose that coffee should be prescribed as consumption of two to four cups (approximately 8 oz each) of drip coffee daily for patients with chronic liver disease. In my practice, I ensure that patients do not sweeten the coffee with large amounts of sugar to avoid excess carbohydrate calorie consumption. I also ensure that patients do not drink coffee to the point at which they feel anxious or jittery, experience palpitations, or lose sleep. These adverse effects generally affect patients who are not coffee consumers. I believe that it is also important to ensure that patients stop consuming other caffeine-containing beverages, from coffee-based milkshake-like "whatever-paccinos" to soft drinks to self-described "energy drinks."

Finally, it is noteworthy that coffee, once considered a negative contributor to health, may actually be one of mankind's good "bad habits." Emerging data showing that coffee is inversely associated with all-cause mortality[7] are highly worthy of our attention, including well-constructed preclinical trials investigating the mechanisms by which coffee drinking may be such a good habit.

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