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Coffee – A panacea or snake oil for the liver?

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United States is the world's biggest consumer of coffee. About 83% of adults drink coffee in the U.S., according to the National Coffee Association's 2013 survey. There has been much interest in the potential health benefits both in scientific journals and lay media. One such example is a study by Freedman which showed a significant, dose-dependent, inverse relationship between coffee and mortality.(1) The benefits spanned a broad range of health conditions: consumption of coffee was associated with reduced mortality not only from heart disease, stroke and diabetes but also infections, respiratory diseases and even accidents.(2) Other studies have shown less impressive results, where in a large prospective European study showed no association between caffeinated, decaffeinated coffee and pancreatic cancer.(4)

With regard to liver health, coffee has been shown to benefit patients with liver disease due to hepatitis C, non- alcoholic steatohepatitis (NASH) and hepatitis B. For example, in a large cross-sectional US study, subjects who consumed more than two cups of coffee a day were much less likely to have chronic liver disease than those who had less than 1 cup a day (hazard ratio (HR)= 0.43).(3) In another population-based study, serum ALT activities were on average 10% lower in subjects who drank three or more cups of coffee daily (5). Regular consumption of three or more cups of coffee daily reduced progression of liver fibrosis in patients with hepatitis C, alcoholic liver diseases and non-alcoholic fatty liver disease.(6,7) Similarly, patients with liver disease consuming more than 3 cups of coffee had less risk of developing hepatocellular carcinoma (HCC), regardless of the etiology of liver disease.(8) These results have been subjected to a systemic review(9), which affirmed that coffee consumption was associated with reduced progression of fibrosis, decreased incidence of hepatocellular carcinoma in cirrhosis and ultimately, lowered mortality.

It remains to be defined whether the type of coffee influences its benefits for the liver. In the study by Freedman, reduced mortality was seen with both caffeinated and decaffeinated coffee.(1) In patients with NASH, regular filtered coffee may be associated with less fibrosis than unfiltered coffee or espresso.(10,11) The filtered coffee has fewer amounts of cafestol and kahweol, compounds associated with increased low-density lipoprotein levels and worsening of steatosis in the liver. (11) The content of anti-angiogenic and anti-oxidant compounds may vary depending upon the preparation methods of the coffee, which might influence the incidence of HCC . (12)

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The exact protective mechanisms of coffee's hepatoprotective effects remain unclear. Out of thousands chemical compounds found in coffee, the chlorogenic acid (belonging to a family of polyphenols which have antioxidant activity), xanthine, and caffeine have been shown to increase the levels of super oxidase dismutase, catalase and glutathione peroxidase. These antioxidant enzymes reduce the levels of oxygen radicals, hydrogen peroxide and peroxide anions which in turn reduces the formation of reactive oxygen species. Recent data suggest that coffee protects against fatty liver disease by stimulating autophagy and increasing mitochondrial beta oxidation, leading to removal of lipids in hepatocytes. (13)

Caffeine has also been shown to increase cyclic monophosphate levels in the hepatocytes by inhibiting phosphodiesterase, which leads to inhibition of TGF- α -mediated proliferation of connective tissue. (14) Finally, caffeine has direct inhibitory effects on hepatic stellate cells by downregulating FAK and actin synthesis.(15) These effects result in decreased deposition of collagenous matrix and reduced progression of fibrosis.

With the backdrop of multitudes of publications indicating favorable impact of coffee in patients with liver disease, the report by Lammert in the current issue of *Clinical Gastroenterology and Hepatology* investigates the association of coffee consumption with primary biliary cirrhosis and primary sclerosing cholangitis. The study found that in comparison to healthy controls, patients with PSC, but not those with PBC, consumed less coffee. In the multivariable logistic regression analysis, current coffee consumption was associated with PSC with an odds ratio (OR) of 0.68 ($p<0.05$) in comparison no present or prior consumption. There was no apparent benefits from prior coffee drinking (OR=1.05). Three quarters of PSC patients had concomitant inflammatory bowel disease (IBD). The protective effects of coffee in PSC patients were most pronounced in patients with IBD. For example, among PSC patients with concurrent ulcerative colitis, coffee was associated with less likelihood of proctocolectomy (HR=0.34, $p<0.01$).

In contrast to the abundant data in parenchymal liver disease, there is paucity of studies about the effects of coffee in cholestatic and autoimmune disorders. It may be useful to note that the genetic influence is higher with these disorders than with common liver diseases such as hepatitis C or alcoholic liver disease. For example, in PSC, there is a 9 to 39 fold increased risk in first degree relatives. Besides IBD which obviously increases the risk of PSC, appendectomy and smoking have been shown to have protective effect in PSC . In a Norwegian cohort study, coffee consumption at 18 years of age was associated with a lower risk of development of PSC (HR=? $p<0.05$). (16)

Based on these data, should one conclude that coffee consumption is protective against PSC? For example, are these sufficient data to support encouraging patients with IBD to consume a certain amount coffee in order to prevent PSC? Well, ideally such a recommendation should be derived from data from randomized trial data. In addition, we would submit that the data by Lammert et al are nowhere conclusive enough to make any changes in our practice.

The most important potential flaw of the study is that it did not specifically take into account the impact of IBD on coffee consumption. A quick survey of information on the Internet

directed towards patients shows that IBD patients are discouraged from drinking coffee because it may irritate the gastrointestinal tract and worsen the IBD symptoms. Although we did not find firm data to establish negative impact of coffee consumption on mucosal inflammation, bowel symptoms, or outcome of IBD, it is not difficult to postulate that IBD patients may avoid coffee because some may have experienced negative consequences from it themselves while others may try to eliminate non-essential food or beverage items from their diet.(17) Regardless, the point here is that if IBD patients are systematically less likely to consume coffee, PSC will have an apparent negative association with coffee consumption. Obviously, in such a scenario, the association merely indicates the result of the disease (IBD) not the cause of PSC. This suspicion is compounded by a couple of aspects of the data. The effect of coffee was limited to current consumption and did not appear to be cumulative, which would be expected if it is causally related. The strong association between coffee consumption and proctocolectomy corroborates the postulate that patients with more severe IBD drink less coffee.

One lesson to be learned from this study for scholars of epidemiological studies is the importance of selecting the right controls in a case control study. Unlike a cohort study in which individuals with and without the exposure event in question (coffee drinking) are derived from the same population and followed to determine who develops disease (e.g., PSC), a case control study may select patients and controls from completely different populations and thus disparate exposure history. For example, the Lammert study recruited from their specialty referral practice, whereas the controls were taken from individuals seeking preventive medical evaluation at Mayo Clinic. The latter group is likely enriched with individuals who are well-educated, affluent, and health-conscious, and thus have a significantly different life style than patients with PSC, for which Mayo is known as a major referral center. This mismatch may not have introduced a huge bias; however, since data that would be needed to take into account in the analysis were not included or reported in the analysis.

Based on the large number of cross-sectional and cohort studies reported to date, there is strong evidence that coffee has hepatoprotective effect in a wide range of chronic liver diseases such as NASH, hepatitis C, cirrhosis, and HCC. However, data to date on cholestatic liver disease are far less certain. It may be that coffee may not be protective of cholangiocytes, the primary locus of damage in PBC and PSC, as it is of hepatocytes. Liver parenchymal damage in those patients may be too removed from the primary events that coffee's benefit is reduced. It may be still possible that coffee *is* beneficial in cholestatic disease; yet, the studies to date may be underpowered or not designed properly to demonstrate the benefits. Regardless, for clinicians, the data are too premature to suggest any changes in our recommendation about coffee consumption in patients with PBC and PSC. For researchers, it will be helpful to understand the mechanisms of the benefits of coffee in hepatocytes versus cholangiocytes, which may lead to randomized trials to evaluate the compounds that drive those benefits.

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