This is important because the sensitivity of blood culture depends on the volume of blood injected into the culture medium. For schoolchildren and adults the recommended volume is 10–15 ml and it is 2–4 ml for toddlers and preschool children.[7,8] If the vaccinators knew which group the participants belonged to, this could have introduced a bias during follow up. The vaccine manufacturers did the serological tests for the study participants and it remains unclear whether the assessment was blinded or not. Finally, it was concluded that Vi typhoid vaccine may contribute to herd immunity. Even though the vaccine protectiveness among the unvaccinated group was 44% (2%–69%), the confidence interval is very wide and it is closer to the null value.

Besides these limitations, there are other factors that should be considered before introducing a new vaccine into a National Immunization Programme.[9] According to WHO, first, the disease should be a public health problem. Is typhoid fever a high priority public health problem in India where the leading causes of under-5 mortality are diarrhoea (20%) and respiratory infection (19%)?[10] Moreover, the introduction of this vaccine would mean an additional visit after 2 years of age, since no vaccines are given at that age under the Universal Immunization Programme (UIP). Currently, immunization coverage in India is still dismal and has high dropout rates. According to the National Family Health Survey-3 (NFHS-3), only 43.5% of children are fully immunized.[11] What would be the impact of the addition of another vaccine on the immunization programme?

Is the typhoid vaccine a good investment? In addition to feasibility studies, a cost-effectiveness analysis would be needed in view of multiple health issues competing for scarce resources in India.

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Coffee and progression of liver disease

Freedman ND, Everhart JE, Lindsay KL, Ghany MG, Curto TM, Shiffman ML, Lee WM, Lok AS, Di Bisceglie AM, Bonkovosky HL, Hoefs JC, Dienstag JL, Morishima C, Abnet CC, Sinha R and the HALT-C trial group. (Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, Maryland; Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles; Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; New England Research Institutes, Watertown, Massachusetts; Hepatology Section, Virginia Commonwealth University Medical Center, Richmond, Virginia; Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas; Division of Gastroenterology, University of Michigan Medical Center, Ann Arbor, Michigan; Division of Gastroenterology and Hepatology, St Louis University School of Medicine, St Louis, Missouri; Departments of Medicine and Molecular and Structural Biology and The Liver–Biliary–Pancreatic Center, University of Connecticut Health Center, Farmington, Connecticut; Division of Gastroenterology, University of California—Irvine, Irvine, California; Gastrointestinal Unit (Medical Services), Massachusetts General Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts; Virology Division, Department of Laboratory Medicine, University of Washington, Seattle, Washington, USA.) Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. *Hepatology* 2009;**50:**1360–9.

SUMMARY

Hepatitis C virus (HCV) is a major cause of chronic liver disease and hepatocellular carcinoma. The prevalence of HCV infection in India has been reported to be around 0.8% in the rural general population[1] and 0.7%–1.8% among blood donors.[2] HCV is the aetiological agent in 14%–26% of patients with cirrhosis and 14%–20% of liver cancers

in India, and its prevalence in these diseases is on the rise. The combination of pegylated interferon and ribavirin, which is the standard therapy available, is effective in achieving sustained virological response (SVR) in just over half the patients with HCV infection.[3] Among patients in whom SVR is not achievable, efforts are made to reduce the ongoing necro-inflammation to lower the risk of progression. Patients with HCV infection and advanced fibrosis or cirrhosis have lower rates of SVR. The hepatitis C antiviral long term treatment against cirrhosis (HALT-C) trial was one such study done among patients with HCV infection and advanced fibrosis, who had previously failed standard therapy, to analyse the outcomes of long term, low dose, pegylated interferon therapy.[4]

In a prospective study, Freedman *et al*. showed that patients with chronic hepatitis C and advanced fibrosis, who had not responded to standard therapy, had a slower progression of liver disease if they consumed higher amounts of coffee. They studied 766 patients from the (HALT-C) trial. These patients were randomized to receive low dose long term therapy with pegylated interferon alpha-2a 90 µg/ week or no treatment. Coffee and tea intake was assessed, using the validated food frequency questionnaire (FFQ). The categories of coffee intake were: never, >0 to <1, ≥1 to <3, ≥3 cups/day over the past year. The patients were followed up prospectively every 3 months and the outcomes looked at were: development of ascites, Child–Turcotte–Pugh score of at least 7, liver disease-related death, hepatic encephalopathy, hepatocellular carcinoma, spontaneous bacterial peritonitis, variceal haemorrhage and an increase of 2 or more points in Ishak fibrosis score on follow up liver biopsy.

The patients were followed up prospectively for 2407 person-years (median 3.8 years per patient; IQR 2.6–2.8). An inverse association was demonstrated between coffee intake and progression of liver disease. Two hundred and thirty patients had evidence of progression of liver disease. The disease progression rates were 11.1/ 100 person years for no coffee intake, 12.1 for <1 cup/day, 8.2 for 1 to <3 cups/day, and 6.3 for ≥3 cups/day of coffee consumption (p for trend=0.001). The crude relative risk (RR) for drinking ≥3 cups of coffee was 0.56 (95% CI: 0.33–0.97) compared with that for non-drinkers and the RR, after adjusting for covariates, was 0.47 (0.27–0.85) for reaching an end-point indicative of disease progression. Interestingly, they also conducted a second FFQ 13 months later and demonstrated that participants reported similar coffee intake in both the baseline and follow up FFQs, suggesting that coffee intake did not change during the observation period. An inverse relationship was also observed between coffee consumption at baseline and lower alpha-foetoprotein (AFP) levels, serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratios, grade of hepatic steatosis, higher albumin levels, lower baseline homeostatic model assessment for insulin resistance (HOMA 2) scores and lower fasting serum insulin levels. However, no such relation was found between intake of tea and progression of liver disease.

COMMENT

Coffee intake has been shown in earlier studies to be beneficial for the liver in terms of lower ALT levels, lower risk of cirrhosis and lower risk of hepatocellular carcinoma among coffee drinkers. In addition, a gradient of this effect has been demonstrated, with drinkers of higher amounts of coffee being protected the most against liver disease.

The benefits of coffee have been ascribed to the presence of a number of constituents of coffee such as caffeine, diterpenes, polyphenols and chlorogenic acid. In a study of 5944 adults who were at high risk of having liver disease, caffeine intake and coffee intake were independently correlated negatively with elevated ALT activity. The association was stronger with caffeine than with coffee intake.[5] Chlorogenic acid has been shown to inhibit the activity of glucose-6-phosphatase, an important enzyme in glucose metabolism which may have an influence on insulin sensitivity.[6] In fact, in the present study, the authors were able to demonstrate an inverse association between coffee intake and serum insulin levels and HOMA scores for insulin resistance. In a prospective study involving 41 836 postmenopausal women, the hazard ratio for death due to inflammatory diseases and cardiovascular diseases was 0.67 (0.5–0.9) and 0.87 (0.6–0.9), respectively, for drinkers of 4–5 cups of coffee per day compared with non-drinkers.[7] This suggests that the constituents of coffee may exert an anti-inflammatory and anti-oxidant effect *in vivo* which may also contribute to its hepatoprotective activity.

Earlier studies, which have shown that coffee consumption is hepatoprotective, have included unselected subjects without any previously known diagnosis of liver disease. In them, subjects with a diagnosis of cirrhosis,[8] chronic liver disease[9] or liver cancer[10] were found to have a lower intake of coffee. Even the ALT levels have been shown to be lower among subjects who drink higher amounts of coffee. In contrast, the present study has for the first time shown that among patients who are known to have advanced liver disease (in this case, HCV-related advanced fibrosis or cirrhosis without SVR to antiviral therapy), coffee consumption is associated with a lower risk of disease progression. The participants were prospectively followed up for several years and evaluated at two time points. The consumption of coffee was shown to be stable between these two observation points. At the end of the observation period, the RR for progression of liver disease was significantly lower among drinkers of >3 cups of coffee per day. There have been other examples where patients of chronic liver disease who have not responded to specific therapies, have beneficial outcomes, if the liver inflammation can be kept under check by the use of non-specific hepatoprotective agents. High dose ursodeoxycholic acid has been shown to reduce ALT levels in patients with chronic hepatitis C infection not responding to interferon.[11] Similarly, long term use of glycyrrhizin among HCV-infected non-responders has been shown to reduce the risk of hepatocellular carcinoma (13% of 244 patients receiving intravenous glycyrrhizin *v*. 26% of 102 patients not receiving glycyrrhizin).[12] Although the results of the present study were seen in a select group of HCV-infected cirrhotics, there seems to be no reason why these results cannot be generalized to other causes of liver disease, since studies have shown the benefit of coffee drinking in non-specifically lowering the risk of cirrhosis, liver cancer and ALT levels.

To conclude, the present study has shown that higher consumption of coffee reduces the risk of disease progression in patients with advanced chronic hepatitis C who have failed to respond to standard therapy. Consumption of coffee was also shown to be associated with less severe steatosis on biopsy, lower insulin levels, AFP levels and AST/ALT ratios. It remains to be seen whether coffee drinking will become a part of a routine prescription by hepatologists.

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