

## **ABSTRACT**

### **Background to the study**

Alcoholic liver disease (ALD) is often associated with dysregulation of iron homeostasis. Previous work from the investigators' group has shown that expression of proteins involved in duodenal iron absorption were down-regulated in patients with ALD. Several factors are known to regulate expression of these duodenal proteins (which include divalent metal transporter 1 [DMT-1], duodenal cytochrome b [Dcytb] and ferroportin). Hepcidin is one such factor. Serum hepcidin levels were decreased in these subjects and, hence, this did not explain the decreased expression of the duodenal proteins. Hypoxia-inducible factor-2 $\alpha$  (HIF-2 $\alpha$ ) in the duodenum is another such regulator, which is known to induce the transcription of these duodenal proteins. Studies done in mice have shown that chronic alcohol ingestion decreased intestinal HIF-2 $\alpha$  levels. However, it is not known whether HIF-2 $\alpha$  expression is altered in patients with ALD.

### **Aim**

To determine protein expression levels of HIF-2 $\alpha$  and gene expression levels of divalent metal transporter 1 (DMT-1), ferroportin and duodenal cytochrome b (Dcytb) in duodenal mucosal samples obtained from patients with ALD and in control subjects.

### **Methods**

Eighteen patients with ALD and 18 control subjects were recruited for the study, after obtaining informed consent. Blood and duodenal mucosal samples were collected from these patients, each of whom underwent a medically-indicated upper gastrointestinal endoscopy. Blood samples were used for estimation of hematological parameters, liver function tests, high-sensitivity C-reactive

protein (hs-CRP) and markers of iron status. The duodenal mucosal samples were used for western blot analysis to determine protein levels of HIF-2 $\alpha$  and for quantitative PCR to determine mRNA expression of DMT-1, Dcytb and ferroportin.

## **Results**

Hemoglobin and total iron-binding capacity (TIBC) were significantly lower in patients with ALD than in control subjects. Serum levels of ferritin and hs-CRP and transferrin saturation were significantly higher in patients with ALD than in control subjects. Protein levels of HIF-2 $\alpha$  and mRNA expression of DMT-1, Dcytb and ferroportin in duodenal mucosal samples were not significantly different in the two groups. HIF-2 $\alpha$  did not correlate with the mRNA expression of any of the duodenal proteins involved in iron absorption.

## **Conclusion**

The results of this study showed that patients with ALD were anemic and showed evidence of systemic inflammation. HIF-2 $\alpha$  was not found to be altered in patients with ALD. However, the sample size of this study was small. An adequate sample size needs to be studied to confirm these findings.

**Keywords:** Alcoholic liver disease, duodenum, HIF-2 $\alpha$ , iron