CHAPTER 4

DISCUSSION

NAFLD is considered to represent the hepatic expression of the Metabolic Syndrome. NAFLD can lead to NASH and subsequent chronic liver disease and cirrhosis. With the increasing prevalence of obesity, coupled with diabetes, dyslipidaemia and hypertension, a very large segment of the population is at risk for impending liver disease in the coming decades. It still remains an active area of research and a better understanding of the pathophysiology of NAFLD would help develop future therapies.

The study examined the possibility that endogenous production of alcohol may be responsible as a part of the 'second hit' theory for the pathogenesis of NAFLD. The fact that alcohol was detected in blood, urine and breath is important evidence for its pathogenesis in the development of NAFLD. This was in keeping with previous animal and human studies. [45,46]

Contrary to previous studies, methanol was also detected. [45, 46] A significantly higher percentage of patients had detectable levels of methanol than ethanol, 55% compared to 35%. No alcohol was detected in the controls, in keeping with the reported non consumption of

alcohol by our patients during their interviews. Of note, no ethanol was detected in the breath of the study subjects, which is not consistent with previous studies. [45, 46] This may be explained by the fact that the intestinally derived ethanol indeed underwent hepatic metabolism, and could not reach the lungs. However, methanol was detected in all body fluids measured. The methanol concentration was highest in blood and significantly higher when compared to that in urine and breath. It is a natural constituent of body fluids. [64] It is available in the diet and sourced principally from vegetables, fresh fruits and fruit juices. Other sources include diet drinks, in which the artificial sweetener aspartame is widely used, and when hydrolysed is partly converted to methanol. The amount of methanol ingested from fruit juices or diet beverages is debatable, but litres would have to be ingested before even being considered to be toxic.[64]

Intestinal bacterial overgrowth has been implicated to explain the increased production of endogenous ethanol. Alterations in gut motility associated with obesity, and complications associated with diabetes, such as visceral autonomic neuropathy, may be responsible for an increase in the intestinal bacterial overgrowth.

This study suggests that importance of endogenous alcohol production may be important in the pathogenesis of NAFLD in patients with the metabolic syndrome. The origin of the alcohol is uncertain, but the importance of intestinal bacterial flora and the role of foods, may be important in the pathology of this disease. If so, it may be that therapeutic alternatives such as the use of antibiotics and probiotics as new treatment strategies may have a role as been alluded to by recent studies.[64]

Rapid weight loss and long lasting fasting periods should be avoided, since they lead to an increase in the flow of NEFA to the liver. A gradual weight reduction is suggested as it is associated with improvement of hepatic lesions, including fibrosis.[65-69]

Control of diabetes, dyslipidaemia and hypertension with diet and drugs, with simultaneous treatment of obesity as suggested above, is of paramount importance.

Oral antibiotics such as metronidazole (flagyl) may be efficacious in reverting steatosis, and in some cases, inflammation and fibrosis. [70, 71] Doses may have to be reduced in severe liver disease. However, side effects such as gastrointestinal intolerance and an unpleasant taste, may affect long term compliance.

Prolong use may also cause a reversible peripheral neuropathy and it is contraindicated in the first trimester during pregnancy.

Probiotics may be a better alternative. They have shown promising results in recent studies. [72-74] They may interfere with the development of NAFLD at various levels: 1) decrease proinflammatory cytokines, 2) alter the inflammatory effects of pathogenic strains of intestinal bacteria, through changes in cytokine signaling, 3) improve epithelial barrier function and thereby avoid excessive exposure of the liver to cytokines and bacterial alcohol. Probiotics have shown to improve liver enzymes in treated patients.

Several cytoprotective agents and antioxidants have shown promising results. These include ursodeoxycholic acid, vitamin E, lecitin, B carotene, selenium, S-adenosyl-methionine, metadoxine and silimarin.[63]

In conclusion, this study therefore suggests that endogenous alcohol production may indeed be responsible for the ‘second hit’ theory in the pathogenesis of NAFLD.