Editorial

Non-alcoholic fatty liver disease and chronic hepatitis B: friends, Foes or strangers

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Non-alcoholic fatty liver disease (NAFLD) represents a growing disease with increasing prevalence throughout the world. This trend is of no exception in the Asia-Pacific region, attributed to socioeconomic changes with adoption of Western lifestyles and dietary habits resulting in increased metabolic syndrome. The prevalence of NAFLD in Asia countries is around 25% (1). Chronic Hepatitis B (CHB) infections affects more than 250 million people worldwide with majorities in Asia countries as well (2).

It is of no surprise that there is increasing prevalence of patients with concomitant NAFLD and CHB. The prevalence of these concomitant diseases varies from multiple studies around the world. In a worldwide meta-analysis study done by Machado et al, the overall prevalence of hepatic steatosis in CHB patients was almost 30% (3). In term of Asian populations, Wong *et al.* reported a prevalence of 13.5% in a study of Hong Kong population (4). In a study from Singapore, 64% of CHB patients have biopsy-proven hepatic steatosis (5).

In this current issue by Fong *et al.*, the prevalence of NAFLD among the studied CHB Asian-American patients was as high as 78%.

To date, the interaction between CHB and NAFLD have been explored in many studies. It was thought that Hepatitis B virus may play a protective role on the development of NAFLD. In a meta-analysis of CHB and NAFLD encompassing studies from China, Hong Kong, Korea and Taiwan, the risk of NAFLD was significantly lower in 8,272 CHB patients than in the 111,631 uninfected controls (6). Fatty liver was diagnosed based on ultrasound in most of these studies in this meta-analysis. In a study by Enomoto *et al.* which included patients with biopsy confirmed hepatic steatosis, there was lower frequency of hepatic steatosis in patients with a high Hepatitis B viral load level (7) while in a meta-analysis study by Machado et al, hepatic steatosis in CHB patients were associated with metabolic factors such as high BMI, diabetes, and hyperlipidaemia (3). Taking these studies into consideration, it can be concluded that the development of NAFLD in CHB patients is probably driven by metabolic risk factors.

The exact interaction between these two concomitant diseases remains elusive. Methods used for the diagnosis of fatty liver have been variable and not consistent across all studies. In this study by Fong *et al.*, controlled attenuation parameter (CAP) score was used for assessment of NAFLD and it is now being used in clinical practice across many countries. While fatty liver can be diagnosed with various non-invasive methods, there is still lack of reliable non-invasive tool to diagnose non-alcoholic steatohepatitis (NASH). An elevated Alanine aminotransferase (ALT) level may not correlate with NASH as studies have showed that patients with raised ALT may not actually have NASH (8). Similarly, patients with fatty liver can also have underlying NASH without an abnormal ALT. A liver biopsy remains the gold standard to confirm the diagnosis of NASH.

Differentiating cause of raised ALT in patient with concomitant diseases

Both CHB and NAFLD can cause an increase in ALT level. Multiple societies and associations' guidelines recommend

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treatment of Hepatitis B if the ALT is more than 2 times the upper limit of normal with raised Hepatitis B viral load, in order to reduce the chances of developing cirrhosis. However, patient with CHB can have raised ALT due to other causes such as NAFLD. In such situations, Hepatitis B viral load may provide a clue in regard to the underlying predominant disease driving the inflammation. Spradling *et al.* looked at 1,090 patients with concomitant fatty liver and CHB and found that NAFLD was the most common cause of raised ALT in patients with low viral load (9). Similar trend was observed as well in a study by Demir *et al.* (10). To date, there is no reliable scoring criteria or serum markers to differentiate between the two conditions. MicroRNA (miRNA) has been studied in patients with concomitant condition (11). Higher level of miRNA: -122, -638, -572 and -575 were seen in patients with NASH and CHB. However, this requires further validation study for clinical utility. However, a liver biopsy remains the best diagnostic method to determine the predominant condition when there is concomitant NAFLD and CHB. If the patient is started on treatment for CHB, current existing evidence showed that the presence of NAFLD does not affect the efficacy of the therapy.

Evaluation of advanced fibrosis or cirrhosis in patients with dual pathology

In study by Fong *et al.*, the FIB-4 was not statistically different in the groups with or without fibrosis.

Although liver biopsy is the gold standard for assessment of fibrosis and cirrhosis, it carries risk of complications due to its invasive nature. Scoring system such as Fibrosis-4 (FIB-4), NAFLD fibrosis score (NFS) and AST to Platelet Ratio Index (APRI) were developed and validated for detection of advanced fibrosis in patients with CHB, Chronic Hepatitis C and NAFLD. However, none of these scores were studied in patient with dual pathology. As ALT is frequency raised in these group of patients, the specificities of these scores may be affected.

Further studies are required for validation.

Progression to liver cirrhosis in patients with concomitant disease

Patients with CHB and/or NAFLD may progress to develop liver cirrhosis. In a retrospective observational study in United States (12), the probability of progression from NAFLD to cirrhosis after 1 year of follow-up was 9%, increasing to almost 40% over the 8 years of the follow-up period. The risk of progression was significantly higher for patients with metabolic risk factors. The rate of progression to cirrhosis in patients with CHB varies according to the level of viral load and Hepatitis B e antigen status. In a prospective study of 256 CHB patients who have liver biopsy obtained, NASH was an independent predictor of advanced fibrosis after adjusting for viraemia levels and features of metabolic syndrome (13). In a study of 459 patients with negative Hepatitis B eAg status, Mak *et al.* found that the presence of hepatic steatosis was associated with fibrosis progression (14). These studies demonstrate possible synergistic effect of NAFLD/NASH on progression to liver cirrhosis in patients with CHB.

Metabolic syndrome is known to increase the risk of liver fibrosis progression in CHB, independent of viral load or hepatitis activity (15). Ye *et al.* reported high prevalence of insulin resistance in patients with both NAFLD and CHB, compared with patients with only NAFLD or CHB (16). Insulin resistance predisposes cells to reactive oxygen particle generation and lipid peroxidation, which subsequently drive the process of liver fibrosis. Aggressive management of insulin resistance and metabolic risk factors may help to prevent progression of fibrosis.

Development of hepatocellular carcinoma (HCC) in patients with concomitant disease

Hepatitis B infection can cause HCC with or without presence of liver cirrhosis. Similarly, NAFLD patients with steatohepatitis may develop HCC in the absence of liver cirrhosis (17). There are conflicting data regarding risk of developing HCC in patients with concomitant disease. In a study from Hong Kong by Chan *et al.*, CHB patients with histologically confirmed NAFLD were found to have 7.3-fold increased risk of developing HCC over a follow-up period of over 7 years (18). In another study by Choi *et al.* with a median duration of follow-up of 10 years, CHB patients with biopsy proven NASH were significantly associated with higher risk of HCC (19). On the contrary, in a study by Lim *et al.* with a median follow-up of 111 months, hepatic steatosis was not associated with higher risk of HCC formation among the patients with CHB (5).

In conclusion, the interaction between CHB and NAFLD remains complicated and there are still unanswered questions to be addressed about their relationship. As

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we step into the era of promising therapies for NAFLD/NASH, it would be interesting to find out how the interplay between these two conditions evolve.

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