

## Non-Alcoholic Fatty Liver Disease (NAFLD)

### Is it an Emerging Risk Factor for Coronary Artery Disease?

Non-alcoholic fatty liver disease (NAFLD) is being recognized as the most common cause of abnormal liver enzymes in the last few decades. It includes a spectrum of liver disorders ranging from simple steatosis to steatohepatitis, fibrosing steatohepatitis, and cirrhosis, which may progress to hepatocellular carcinoma; however, the most common cause of death in patients with NAFLD is coronary artery disease (CAD), not chronic liver disease.<sup>1</sup>

The prevalence of NAFLD is more common in type 2 diabetic patients (70-80% in comparison to 20-30% in the general population), who are also at higher risk of developing advanced fibrosis and cirrhosis.<sup>2</sup> NAFLD is regarded as the hepatic manifestation of the metabolic syndrome, since as many as 90% of NAFLD cases have at least one component of the metabolic syndrome and as many as 33% have three or more components.<sup>3</sup> It is related with more severe insulin resistance and hypoadiponectinemia in the patients of metabolic syndrome.<sup>4</sup> It may respond to treatments originally developed for other insulin-resistant states (e.g. diabetes mellitus type 2) such as weight loss, metformin and thiazolidinediones.<sup>5</sup>

The relationship of NAFLD with CAD is independent of classical risk factors and is only partly explained by occurrence of metabolic syndrome.<sup>6,7</sup> In patients with clinical indications for coronary angiogram, fatty liver is associated with coronary artery disease independently of other metabolic factors.<sup>8</sup> NAFLD has been associated with an abnormal coronary flow reserve (CFR), which is widely used to examine the integrity of coronary microvascular circulation and liver fibrosis scores are found to be an independent predictor of depressed CFR.<sup>9</sup> NAFLD has been considered a novel risk factor for vulnerable coronary plaques,<sup>10</sup> and has been associated with the increased score (>100) of coronary artery calcification.<sup>11</sup> Because of the high risk of atherosclerosis in patients with NAFLD, even without metabolic syndrome, assessment of NAFLD may be helpful for cardiovascular risk stratification.<sup>12</sup> It might be beneficial for the NAFLD patients to undergo screening of metabolic syndrome as well as intima media thickness in order to assess the future atherosclerotic complications.<sup>13</sup> NAFLD could not merely be a marker of cardiovascular disease (CVD), but may also be actively involved in its pathogenesis, which includes a release of pro-atherogenic factors from the liver (C-reactive protein, fibrinogen, plasminogen activator inhibitor-1, IL-6 and other inflammatory cytokines), hepatic insulin resistance, subclinical inflammation and atherogenic dyslipidemia which together lead to increased oxidative stress and endothelial dysfunction, finally promoting CAD.<sup>1,14</sup> However, more detail studies are required to understand the role played by NAFLD in the pathogenesis of coronary artery disease.

Umid Kumar Shrestha<sup>\*a</sup>

<sup>a</sup> Manipal College of Medical Sciences, Pokhara, Nepal

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#### \*Corresponding author

*Department of Internal Medicine, Manipal College of Medical Sciences and Manipal Teaching Hospital, Phulbari-11, Pokhara, Kaski, Nepal  
Email address - umidshrestha@gmail.com*

When NAFLD is superimposed on classical risk factors, the risk of CAD may further increase. A multidisciplinary approach is necessary to control the cardiovascular and liver complications related with NAFLD.

NAFLD may be an emerging risk factor, independent to the classical risk factors and can be utilized as a surrogate marker

to predict CAD. However, well-designed intervention studies, randomized clinical trials and long-term follow-up studies on large representative patients with NAFLD are needed to assess the development of coronary artery disease over a period of time; these studies might help to explain the temporal evolution of NAFLD, metabolic syndrome and coronary artery disease.

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