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EDITORIAL

Long live the Liver!

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As the new-fangled COVID-19 pandemic begins to recede, the spectre of the old and familiar pandemic of obesity looms large once again. Of the many diseases, obesity predisposes to one of the most sinister albeit silent is non-alcoholic fatty liver disease.

The recent worldwide prevalence estimates of NAFLD are alarming to say the least. A meta-analysis published in July 2022 estimates the NAFLD worldwide prevalence to be 32.4% with a suggestion of a rapid increase in the past decade [1]. The numbers in patients with diabetes are even more unsettling. The NAFLD prevalence in patients living with type 2 diabetes mellitus is more than twice that of the general population. A 2019 meta-analysis pegs the prevalence of NAFLD in type 2 diabetes mellitus to be 55.5% [2].

Closer home, while the data may not be that extensive, the numbers here are far from reassuring. Data on overall prevalence of NAFLD in India is scanty—small studies suggest that the prevalence ranges between 8 and 32% [3]. Notably, most of these studies are from the past decade and do not take into account the temporal effects observed in the Western data. Hence, it may be wise to assume a much higher current prevalence of NAFLD.

In a recently published study from India, a review of electronic medical records of more than 1.5 lakh patients with diabetes suggests that 44.48% of them have NAFLD, the prevalence being close to 60% for males [4].

The link between NAFLD and diabetes appears to be sinister. Insulin resistance is proposed to be a major player in the pathogenesis of NAFLD. Increase in lipolysis, de novo triglyceride synthesis, hepatic triglyceride uptake and accumulation are consequences of insulin resistance which promote NAFLD. Features of metabolic syndrome (MS) are present in most patients with NAFLD—some authors refer to NAFLD as the hepatic manifestation of MS [3]. The close association between NAFLD and other metabolic factors explains the high prevalence of NAFLD in diabetes.

It is however interesting to study which type 2 diabetes patients are likely to develop NAFLD. In a study from Brazil, patients with diabetes and NAFLD had more obesity, waist circumference, hypertriglyceridemia and elevated alanine transaminases as compared to those without NAFLD [5]. A large data set from Italy suggests that patients with diabetes and NAFLD are likely to be older and have higher age adjusted prevalence of macrovascular complications when compared with those with diabetes but without NAFLD [6]. Interestingly, a small study from Sri Lanka found that patients of diabetes who had NAFLD were younger than those without NAFLD. Increased BMI, waist circumference and transaminitis were present in those with NAFLD [7]. Among patients with diabetes with normal aminotransferases, those with NAFLD had worse HbA1c and higher insulin resistance than those without NAFLD [8].

In this issue, Ayaz et al. [9] studied diabetes patients with and without hepatic steatosis. Surprisingly, they found that glycemic status was not significantly different between the two groups. Previous studies have reported positive correlation between HbA1c and NAFLD in both diabetes patients and those without diabetes [10, 11]. This discrepancy probably hints at the now well-known concept of type 2 diabetes being a heterogeneous group of disorders rather than a single disease. Novel subtypes of type 2 diabetes have now been identified. Some of these subtypes have less insulin resistance and more decrements in insulin secretion. If insulin resistance is the underlying cause of NAFLD, the insulin deficient subtypes may not share the burden of NAFLD equally. More studies on subtypes of diabetes and NAFLD would be informative.

Keeping the heterogeneity of diabetes in mind, racial factors are important in NAFLD as well. Asian Indians can have nearly two times higher hepatic fat for the same BMI when compared with Caucasians [12]. Petersen et al.similarly reported two times higher hepatic triglyceride content and IL-6 levels in Asian Indians as compared to Caucasians [13]. This suggests that in our country, type 2 diabetes

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mellitus with NAFLD would be a common clinical scenario. Not only do we, as physicians involved in diabetes care, need to understand this in detail to better manage our patients, but there is also a need to further characterize our diabetes clusters to see if those with NAFLD emerge as a unique cluster with distinct pathogenesis, natural history and prognosis.

Other factors in the pathogenesis of NAFLD also need to be explored. Depletion of antioxidants such as vitamin E, vitamin A and glutathione may lead to hepatic inflammation. In this issue, Saber et al. demonstrate that in an animal model of NAFLD, the levels of vitamin A, vitamin E and selenium reduce significantly as compared to controls. Other data has looked at role of hormones, such as leptin and adiponectin, and incretins as well as intestinal microbes and bile acids in pathophysiology of NAFLD. These and other studies on pathophysiology are important as they provide vital clues on developing therapeutic options for NAFLD. Although the mainstay of NAFLD therapy continues to be lifestyle intervention and weight reduction, several pharmacotherapeutic measures are now available. Vitamin E has shown promise in therapy of non-alcoholic steatohepatitis (NASH) in patients without diabetes [14]. Similarly, biopsy-proven NASH appears to respond well to pioglitazones [15]. These pharmacotherapeutic measures have been shown to be beneficial in biopsy-proven NASH, but their utility in other milder forms of NAFLD has yet to be demonstrated. Metformin, omega-e fatty acids, obeticholic acid and ursodeoxycholic acids are other drugs which have shown possible benefit [16]. More recently, data on potential benefits of diabetes medications including SGLT-2 inhibitors and GLP-1 analogues has emerged [16]. As these drugs cause significant weight reduction and improve glycemic control, these findings were not unexpected. Although this data is still evolving, semaglutide has shown improvement in cases of biopsy-proven NASH [17]. While conclusive evidence is awaited, it is prudent to prioritize these drugs in the treatment of patients with co-existent diabetes mellitus and NAFLD.

The silent nature of NAFLD often results in the disease being ignored in its initial stages. However, once inflammation progresses, this disorder can lead to serious morbidity as well as mortality. While on one hand efforts to elucidate the pathophysiology and management aspects of NAFLD need to be expedited, the benefits of the same cannot be harnessed unless the awareness of this disorder grows.

Healthcare providers at all levels need to be sensitized about the looming threat on the liver so that appropriate advice and screening can be provided to patients. Keeping obesity in check, eating a healthy diet and exercising regularly can have myriad benefits including reduced risk of NAFLD. As is true for other lifestyle disorders, for NAFLD, prevention would be much better than cure.

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