METABOLISM CLINICAL AND EXPERIMENTAL 65 (2016) 1096–1108

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Non-alcoholic fatty liver disease and diabetes

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ARTICLE INFO

Article history:
Received 30 July 2015
Accepted 5 January 2016

Keywords:
NAFLD
NASH
Diabetes
Insulin resistance
Diabetes complications

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) are common conditions that regularly co-exist and can act synergistically to drive adverse outcomes. The presence of both NAFLD and T2DM increases the likelihood of the development of complications of diabetes (including both macro- and micro- vascular complications) as well as augmenting the risk of more severe NAFLD, including cirrhosis, hepatocellular carcinoma and death.

The mainstay of NAFLD management is currently to reduce modifiable metabolic risk. Achieving good glycaemic control and optimising weight loss are pivotal to restricting disease progression. Once cirrhosis has developed, it is necessary to screen for complications and minimise the risk of hepatic decompensation.

Therapeutic disease modifying options for patients with NAFLD are currently limited. When diabetes and NAFLD co-exist, there are published data that can help inform the clinician as to the most appropriate oral hypoglycaemic agent or injectable therapy that may improve NAFLD, however most of these data are drawn from observations in retrospective series and there is a paucity of well-designed randomised double blind placebo controlled studies with gold-standard end-points. Furthermore, given the heterogeneity of inclusion criteria and primary outcomes, as well as duration of follow-up, it is difficult to draw robust conclusions that are applicable across the entire spectrum of NAFLD and diabetes. In this review, we have summarised and critically evaluated the available data, with the aim of helping to inform the reader as to the most pertinent issues when managing patients with co-existent NAFLD and T2DM.

1. Introduction

1.1. NAFLD is Common Among Individuals with Type 2 Diabetes

The prevalence of NAFLD varies widely depending on the population studied and the methodology applied. Studies have shown that NAFLD may be present in up to 70% of patients with diabetes [1,2] whilst the prevalence of biopsy proven NASH (non-alcoholic steatohepatitis) in asymptomatic type 2 diabetics with normal liver function tests (LFTs) was 20% [3]. Estimates from our own studies and others have suggested that there is a significant burden of advanced fibrosis in asymptomatic individuals with type 2 diabetes ranging from 5% to 7% [4,5]. There is therefore no doubt that these two common conditions co-exist and that there is significant amount of unrecognised

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http://dx.doi.org/10.1016/j.metabol.2016.01.001

advanced NAFLD within asymptomatic diabetic patients. Obesity and physical inactivity are interlinked risk factors for the development of diabetes and both are clearly implicated in an individual's risk of developing NAFLD. In a large cross-sectional study an individual's sitting time was associated with NAFLD diagnosed using US and interestingly this association held true in those with a normal BMI [6]. Obesity is well known to correlate with both NAFLD prevalence and severity. In a study of patients who had liver biopsies whilst undergoing elective abdominal surgery the BMI was strongly correlated with NASH [7] and in a separate study intraabdominal fat was associated with NASH [8].

1.2. *NAFLD Increases Diabetes Risk, But the Reciprocal Relationship is Less Clear Cut*

There is a strong association between NAFLD and diabetes risk. An individual's risk of developing diabetes is increased approximately 5-fold if they have NAFLD, although this is dependent on the population studied, duration of follow-up and methodology used to diagnose NAFLD [9–23] (Table 1). There is a considerable degree of heterogeneity among these studies and in one of the longest prospective studies, the observed increased risk for developing type 2 diabetes (19% vs 6% for non-NAFLD) was found to be non-significant after adjusting for confounding variables. However, the diagnosis of NAFLD at baseline was made on the basis of abnormal LFTs without imaging and it is therefore likely that some individuals classified as non-NAFLD may have had a degree of hepatic steatosis or even more advanced disease [24]. Importantly, improving NAFLD has been shown to modify the risk of developing diabetes [25]. Currently, we are not able to predict which individuals with NAFLD will develop diabetes and annual surveillance of HbA1c is likely to be the most pragmatic solution although some data suggest that an OGTT may be more accurate in the context of NAFLD reflecting post-prandial glucose excursions [26,27].

Whether type 2 diabetes increases an individual's risk of developing NAFLD is less clear cut and harder to study. A large proportion of patients with type 2 diabetes are diagnosed long after the onset of their diabetes which means that it is difficult to design studies assessing the duration of diabetes and the risk of developing NAFLD although common sense would dictate that there is a positive association. Given the insidious nature of type 2 diabetes, it is not surprising that those with established diabetes have markedly more liver fat when compared to age, BMI and gender matched controls [28]. However in cross-sectional analysis of 99,969 apparently healthy, non-diabetic Korean individuals, there was an increased risk of NAFLD (as determined by USS (ultrasound scan)) with increasing levels of HbA1c and insulin resistance, independent of obesity [29]. This introduces the concept of 'pre-diabetes' as a possible precursor for NAFLD and its subsequent progression. A small cross-sectional series of non-diabetic individuals found that impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) alone occurred in 25% of patients with simple steatosis versus 55% of those with NASH [30]. In a study of 108 patients with serial liver biopsies (median interval 6.6 years) at baseline those with NASH rather than NAFL were more likely to be diabetic (56% vs 21%) and importantly those who had advanced fibrosis or cirrhosis at follow up biopsy were more likely to be diabetic at follow up than those without advanced fibrosis (89% vs 47%) [31]. Taken together these findings highlight the importance of diabetes to NAFLD disease progression.

Whilst insulin resistance is implicated in NAFLD pathogenesis there is still continued debate as to whether this represents a cause or consequence [32]. Conversely, some studies have shown that NAFLD risk may actually be lower in patients with type 1 diabetes in comparison with controls, however in these studies, differences in visceral adipose, lipid profiles and LFTs in the control cohorts as well as the high prevalence of NAFLD in overweight asymptomatic individuals may mask any increased risk [33,34]. However, these observations are supported by a paediatric study where the control individuals and patients had similar lipid profiles, although it should be noted that the differences in hepatic lipid percentage was small [35].

1.3. *NAFLD Increases Risk of Diabetes Complications and Diabetes May Increase the Risk of NAFLD Progression*

NAFLD (diagnosed on ultrasound and excluding other causes of liver disease) increases the risk of cardiovascular events by 1.87-fold of an individual with type 2 diabetes after adjusting for confounders [36]. Although a separate study did not identify increased mortality, in this retrospective analysis the cohort investigated was composed of those who underwent CT scanning for a specific clinical indication and this may have had an additive effect on mortality risk, potentially masking any impact of NAFLD [37]. It is important to recognise that neither of these studies used liver biopsies and as a consequence was not able to differentiate between NAFLD and NASH which may be relevant to cardiovascular disease risk [38]. As well as cardiovascular risk [36], co-existent NAFLD increases the risk of microvascular complications of diabetes including chronic kidney disease and retinopathy [39]. Furthermore, hepatic fat content has been shown to be associated with increased insulin requirements [40] which have the potential to fuel weight gain. The available data linking NAFLD to diabetes complications are limited in that they are mostly taken either retrospectively or from observational cohort studies rather than from longitudinal data.

There is emerging evidence demonstrating an additive detrimental liver outcome for people with co-existent diabetes and NAFLD. A diagnosis of diabetes makes an individual more likely to have more severe NAFLD with the associated complications of cirrhosis and mortality. In one large cohort study, the standardised mortality ratio from cirrhosis was increased in diabetics (2.52) [41]. Furthermore, in a series of 432 patients with biopsy proven NAFLD the presence of co-existent type 2 diabetes was found to be an independent risk factor for fibrosis [42]. Other smaller studies that included liver biopsies have identified an additive effect of NAFLD and diabetes on cirrhosis, liver and all-cause mortality [43]. In another study, those patients with periportal–portal fibrosis were more likely to have diabetes [44]. In studies using serial biopsies those with progressive fibrosis were more likely to be diabetic at baseline and were also more likely to develop diabetes if not already diagnosed [31,45]. Finally, in a meta-analysis, co-existent diabetes was associated with a poorer prognosis in individuals with hepatocellular carcinoma [46]. Overall therefore, the evidence seems clear that co-existent NAFLD and diabetes are associated with a more severe adverse outcome than either of the conditions in isolation.