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Non-Alcoholic Fatty Liver Disease in Patients with Diabetes Mellitus: A Clinician's Perspective

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Abstract

Nonalcoholic fatty liver disease with its phenotypes fatty liver and steatohepatitis, is the most common cause of chronic liver disease worldwide and linked to the epidemic of diabetes mellitus and obesity. It is characterized by a high cardiovascular and liver-related mortality and expected to soon become the leading cause for liver transplantation. This concise review summarizes recent progress in the clinical management of patients with diabetes mellitus and nonalcoholic fatty liver disease and evaluates strategies to manage diabetes mellitus in terms of their effectiveness towards this epidemic liver disease.

Keywords: NAFLD; NASH; Insulin resistance; Hepatocellular carcinoma; Cryptogenic cirrhosis; Physical activity; Life style; Diet; Metformin; Thiazolidinediones; Nuclear receptor agonists

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Scope of the Problem

More than 25 million Americans are afflicted with diabetes mellitus [1], a common public health challenge worldwide expected to affect by 2030 nearly 600 million or more than 9% of the adult population [2, 3]. Type 2 diabetes mellitus, characterized by insulin resistance, accounts for more than 90% of diabetes forms and is now considered to represent the seventh leading cause of death in the US. A population-based study of diabetic patients living in the Social Health Unity of Verona showed that patients with diabetes mellitus had a higher mortality when compared with the general non-diabetic population [4]. More detailed analysis revealed that approximately 4% of all-cause mortality is liver-related [5]. It is now well established that nonalcoholic fatty liver disease (NAFLD) is key to the known link between diabetes mellitus and liver mortality. The pathophysiological link between NAFLD and diabetes mellitus is beyond the scope of this review and has been reviewed in detail elsewhere [6]. Of note, development of NAFLD with progression to nonalcoholic steatohepatitis (NASH) on one hand and diabetes mellitus on the other hand involves alterations of several shared metabolic pathways in addition to environmental factors, genetic predisposition and epigenetic factors.

NAFLD, the most common liver disease worldwide, occurs in two distinct phenotypes that can be distinguished only based on liver histology, simple steatosis and NASH, respectively. Of these two phenotypes, only patients with NASH have a higher mortality over a period of up to 20 years when compared with the general population [7, 8]. In this regard it is of great importance to understand that histologic features of NASH appear to be most relevant to short-term disease progression whereas the presence of liver fibrosis indicates a higher likelihood of dying or developing liver-related complications within one or two decades [9]. Unfortunately many subjects with NAFLD remain undiagnosed as many primary care providers and hospital specialists underestimate the prevalence of NAFLD in their patient population [10-13]. Paradoxically this holds particularly true for cardiologists and endocrinologists albeit NAFLD is most prevalent in type 2 diabetes mellitus and coronary artery disease, respectively [14, 15]. Contributing to this is the fact that patients with NASH can have entirely normal plasma aminotransferases [16, 17]. This observation has recently been confirmed for patients with diabetes mellitus [18]. In addition, providers still have the misconception that improving diabetes control alone will be sufficient to improve the natural history of NAFLD and therefore make NASH targeted treatment unnecessary. Interestingly, there is a low awareness of NAFLD in the general population as well as among patients with metabolic risk factors [19, 20]. Implementing early prevention strategies and optimizing care is desired but will fail without systematic screening in asymptomatic high risk subjects and advanced liver disease will not be diagnosed.

The purpose of this review is to increase the awareness of NAFLD in patients with diabetes mellitus, to explore the impact of diabetes therapy on NAFLD and to highlight new treatment avenues that benefit patients with both, NAFLD and diabetes mellitus, respectively.

Diabetes Mellitus, NASH, Liver Cirrhosis and Hepatocellular Carcinoma

The prevalence of NAFLD in the general US population is estimated to be 34% [21], 34-74% in patients with diabetes mellitus [22] and 100% in obese patients with diabetes mellitus [23]. Diabetes mellitus is an independent risk factor for NAFLD and the risk appears to increase by 10-20% per rising mmol/l fasting glucose levels [24, 25]. In patients with diabetes mellitus, the diagnosis of NAFLD is usually made within 6 years after diagnosing diabetes [26]. Although the natural history of NAFLD is incompletely understood, it was thought that approximately 20% of patients with diabetes mellitus will develop NASH [27]. This is being challenged by the recent observation that 56% of diabetics with normal aminotransferases had biopsy-proven NASH [18]. The interactions between diabetes and NAFLD are complex and it has been shown that NAFLD is associated with an 3-5 fold increased risk to develop diabetes [28, 29]. On a time scale diabetes may be diagnosed up to 4 years after diagnosis of NAFLD [26]. Of note, improvement of NAFLD has the potential to reduce the incidence of diabetes as has been shown in a recent retrospective 10 year follow-up study [30].

For reasons that are incompletely understood, only a portion of patients with NASH progress to liver cirrhosis. At the stage of cirrhosis, steatosis often disappeared supporting the notion that nearly 40% of previously diagnosed cryptogenic cirrhosis is recognized as NAFLD or burned-out NASH [31]. A large number of patients with cryptogenic cirrhosis have diabetes mellitus [32], again consistent with NASH leading to liver cirrhosis. Insulin resistance is present in up to 80% of patients with liver cirrhosis, irrespective of the etiology of cirrhosis [33]. Whereas insulin resistance and diabetes mellitus can develop as the liver function deteriorates [34, 35], it is believed to play a central role in the development of NAFLD.

For the past almost two decades it has been known that there is a three-fold risk of hepatocellular carcinoma (HCC) in patients with diabetes mellitus that do not have liver cirrhosis or other concomitant diseases that predispose to liver cancer [36]. The increased prevalence of hepatocellular carcinoma in patients with diabetes mellitus as well as the increased prevalence of diabetes mellitus in patients with liver cancer also suggests that NASH can lead to liver cancer in the diabetic population [37, 38]. Although the majority of HCC's appear to arise in cirrhotic livers with an estimated incidence of 2-3% per year, a substantial proportion of cancers may occur in the absence of advanced fibrosis [39, 40]. A detailed characterization of these HCC's and patients is of critical importance to allow a better targeted HCC surveillance in NAFLD.

Examining the cause-specific mortality in patients with diabetes revealed that liver cirrhosis was a leading cause of death accounting for 4% of deaths. Compared with the general population the risk of dying due to cirrhosis was doubled [5]. In another European cohort of diabetics, liver cirrhosis accounted for 12.5% of deaths [41], confirming a link the between diabetes mellitus and liver cirrhosis described by Creutzfeldt more than forty years ago [42]. Although less common, type 1 diabetes mellitus also appears to be linked to a nearly 2-fold increase in liver cirrhosis when compared with the general population [43]. Notably, liver-related outcomes among patients with type 1 and type 2 diabetes mellitus were similar in this study.

NAFLD, Diabetes Mellitus and Cardiovascular Disease

Current evidence supports that NAFLD, irrespective of the methodology used to diagnose NAFLD, is associated with an increased risk of cardiovascular events in both non-diabetic and type 2 diabetic individuals. At first, this link will be attributed to the fact that NAFLD often presents with features of the metabolic syndrome that represent established risk factors for cardiovascular disease [44]. However, a growing body of evidence suggests that NAFLD and in particular its necroinflammatory state, NASH, is independent of classic risk factors associated not only with markers of subclinical atherosclerosis but also incident cardiovascular disease [45-48]. These observations are in support of cardiovascular events being the leading cause of death in NAFLD [7, 8, 49, 50]. The biologic mechanisms involved in the increased cardiovascular risk are yet to be worked out. It is however likely that multiple players contribute to the increased cardiovascular risk, including pro-inflammatory markers and a pro-thrombotic state.

Due to the high risk for future cardiovascular events, patients with NAFLD should deserve special attention for cardiovascular screening and surveillance strategies. Although this strategy may lead to early intervention with improvement of prognosis, long-term studies to validate the value if ameliorating NASH will result in prevention of cardiovascular events are needed.

Genetic Basis of Diabetes Mellitus and NAFLD

Genome wide association studies that evaluate the genotypic-phenotypic association in population-based cohorts have been performed in NAFLD [51]. Numerous genetic variants of cytokines and adipocytokines as well as genes influencing lipid metabolism, insulin signaling, oxidative stress, fibrogenesis and inflammation may account for the variability in susceptibility to NAFLD [52]. Only a small number of single nucleotide polymorphisms are linked to diabetes mellitus and NAFLD. TCF7L2 and GCKR appear to reflect an increased risk for diabetes mellitus and NAFLD [53-55]. Among genes involved in lipid metabolism, APOB, APOC3 and MTTP [51] have been associated with diabetes mellitus and NAFLD whereas a sterol regulatory element-binding factor 2 polymorphism could predispose lean and non-diabetic subjects to develop not only NAFLD but also diabetes mellitus [56].

However, most of these genetic variants have not been validated by replication cohorts and, when compared with epigenetic modifiers [57], may affect only a small proportion of NAFLD phenotypes. It appears logic to assume that several genes are involved and interlinked in the pathogenesis of diabetes mellitus and NAFLD with a specific phenotype regulated by genes involved in diverse metabolic pathways. Novel information may be obtained by exploring the association of variation within multiple genes

involved in a defined biologic pathway with a given phenotype [58]. Furthermore, information may be gained to determine to what degree constitutional genome variability within biologic processes promotes disease progression or response to treatment. Clearly, large collaborative studies including ethnically and geographic diverse populations are needed.

Diagnosis of Non-alcoholic Fatty Liver Disease

Diagnosis of non-alcoholic fatty liver disease requires demonstration of fatty liver in the absence of significant alcohol use (<30 g per day for men; <20 g per day for women) and other coexisting liver diseases or other causes inducing fatty liver [59]. Therefore NAFLD clearly is a diagnosis of exclusion by employing clinical, laboratory and imaging studies. The image modality of choice to document the presence of fatty liver is abdominal ultrasound. It is widely available, portable, not associated with radiation exposure, non-invasive and not costly. It is ideally suited to examine large numbers of patients. The only caveat is the lack of sensitivity for less than 20-30% of fat and the low precision in grading NAFLD [60, 61]. More accurate quantification of intrahepatic fat to detect even mild degrees of steatosis can be achieved with other imaging modalities such as computed tomography and magnetic resonance [62] but those modalities are expensive and not practical for routine use and screening of a larger number of subjects. Until today, no imaging techniques can reliably distinguish between steatosis and steatohepatitis.

Assessment of Disease Severity

Assessing disease severity becomes of particular importance as identifying patients with advanced fibrosis and cirrhosis allows screening for liver-related complications such as liver cancer. Current diagnostic standard is to perform a liver biopsy as it is the only reliable test to distinguish between simple steatosis and NASH while at the same time providing information regarding the extent of fibrosis. Liver biopsy, however, has clear limitations which include the invasive nature of the procedure with potential associated complications [63], sampling error particularly for small biopsy samples with underestimating disease severity [64], variability in pathologist interpretation, cost and inability to be performed in the clinic.

Research over the last years has attempted to substitute liver biopsy with a noninvasive test that would allow accurate diagnosis, grade and stage of nonalcoholic fatty liver disease. It is well established that advanced fibrosis can be present in patient with NAFLD that display mildly elevated or even normal liver enzymes [17, 65, 66]. Therefore liver enzymes such as ALT are not a good marker for disease stage. Serum IgA levels are lower in simple steatosis compared with NASH, particularly in patients with diabetes mellitus. In addition, serum IgA levels are an independent predictor of advanced fibrosis [67], yet there is no clear cut threshold to allow distinguishing between steatosis and NASH. Several scoring systems based on laboratory tests or clinical findings have been evaluated and compared with liver biopsy [66, 68]. None of the scoring systems is helpful to differentiate between simple steatosis and NASH, but each of them is able to reliably exclude advanced fibrosis in NAFLD and help avoid a significant number of unnecessary liver biopsies. Unfortunately, these scoring systems did not perform well in the Edinburgh type 2 diabetes study [69]. This is surprising but may reflect aggressive treatment of diabetes [70] or a low prevalence of advanced fibrosis. Perhaps each scoring system requires its own range reflecting a specific population. On the other hand, routinely available clinical and biochemical factors obtained in patients with diabetes can help accurately classify 67% and 77% of diabetic patients with NASH and advanced liver fibrosis, respectively [71].

Elastography or liver stiffness measurements for assessment of disease activity (inflammation) and severity (fibrosis) have been explored in NAFLD employing ultrasound based transient elastography, acoustic radiation force impulse imaging and magnetic resonance elastography [72]. It is anticipated that particularly the new ultrasound based imaging modalities will be adopted in clinical practice rapidly clearly helping to avoid unnecessary liver biopsies. However, as the relative contributions of inflammation and fibrosis to liver stiffness measurements remain unknown, these tests unlikely can be used to monitor treatment response. Liver stiffness measurements with concomitant assessment of liver fat by assessing the controlled attenuation parameter is currently the most advanced noninvasive testing that could be used for screening diabetic and other high risk patients [73].

Employing high-throughput analysis based on genomics, lipidomics, proteomics and metabolomics in the post genomic era, will yield a wealth of information and provide a unique perspective of disease processes. It is hoped that these approaches will help identify biomarkers to not only accurately diagnose the various stages of NAFLD, but also to predict outcomes and responses to effective treatment once available [74].

Clinical Management

Although risk factors for NAFLD are well stablished, exact mechanisms that determine progression from pure steatosis to steatohepatitis and ultimately cirrhosis remain incompletely understood. Despite emerging novel therapeutic targets for NAFLD therapy [75], life style modification including diet and physical activity accompanied by drug therapy of diabetes mellitus remains the foundation how diabetic patients with NAFLD are currently managed.

Life style modification

Patients with diabetes mellitus and NAFLD are often overweight and therefore lifestyle interventions to achieve weight loss should play an important role in disease management. Of note, weight loss should be controlled and not too fast to avoid worsening of liver injury [76]. Reducing energy intake while maintaining a healthy diet will facilitate weight loss, particularly when combined with physical activity. Physical activity is an important part of the diabetes management plan [77]. Of note, a reduction in visceral fat and improvement of insulin sensitivity can already be achieved with minimal weight loss [78-81]. It is now recommended to perform a moderate-intensity physical activity (50–70% of maximum heart rate) at least three times per week for a total of at least 2.5 hrs [82-84]. However, patients with NAFLD have a low compliance with physical activity often due to fatigue [85].

The Western-style diet of patients with NAFLD is characterized by a high content of fructose corn syrup and saturated fatty acids whereas mono- and polyunsaturated fatty acids, fiber and antioxidants are less present [86-88]. Unlike glucose, fructose does not stimulate insulin or leptin secretion, effectively bypassing normal satiety signals and contributing to the observed increased caloric intake in patients with NAFLD [89]. In contrast, a Mediterranean diet rich in mono- and polyunsaturated and fatty acids may reduce liver fat and improve insulin resistance even without weight loss [90]. No specific dietary guidelines exist for NAFLD, but it is plausible that dietary recommendations for diabetes mellitus apply for NAFLD although their utility for treating NAFLD remains largely unknown [91]. In agreement with recommendations of the American Diabetes Association [77], patients with NAFLD should minimize or even avoid the consumption of high fructose corn syrup whereas the amount of consumed complex carbohydrates found in whole grains, legumes and vegetables should be increased. Limiting the dietary content of saturated fat (<7% of total calories) by increasing the amount of mono- and polyunsaturated fatty acids may be beneficial for NAFLD patients by promoting a favorable lipid profile, improving glucose levels and reducing liver inflammation and steatosis, respectively [92-94]. Until studies in the diabetic population with NAFLD as outcome are available to establish evidence-based guidelines, one can propose a dietary framework for patients with NAFLD that extrapolates from dietary guidelines aiming to improve insulin resistance [95].

Although an optimal strategy has not yet been worked out, sustainability of these modifications is paramount to their success but often difficult to accomplish and may require concomitant cognitive-behavioral approaches [96, 97]. It is also important to realize that many patients face barriers to success such as immobility, work schedules, limited access to quality food and an unsupportive environment, respectively. To promote long-term lifestyle modifications it appears equally important that patients will not only undergo an initial comprehensive counseling but also monitoring and ongoing evaluations with modifications of interventions as needed. Carefully designed and executed intervention trials in diabetic patients with NAFLD should provide the basis for future evidence-based lifestyle interventions.

Insulin sensitizing agents

Insulin resistance is a key pathophysiological factor in the development of NASH. Efforts to improve insulin sensitivity as therapeutic intervention is therefore not surprising and should be a primary goal, irrespective of the presence or absence of NAFLD as effective glucose control reduced complications in diabetes mellitus. Current standards of medical care in type 2 diabetes mellitus recommend the biguanide metformin as preferred initial pharmacological agent. The glucose-lowering effects of metformin are due to lowered gluconeogenesis, increased glucose uptake into muscle and increased fatty acid oxidation in adipose tissue, all considered due to activation of adenosine monophosphate-activated protein kinase [98]. Several small clinical trials using metformin are supporting a beneficial role in NAFLD [99]. These studies however were small in number, using different drug doses, employing diabetic and non-diabetic patients at various disease stages with limited available data to demonstrate histological improvement. Therefore larger randomized controlled trials of sufficient duration using clearly defined histological endpoints are needed to fully assess potential drug efficacy in modifying the natural history of NAFLD [59]. These studies may also be able to demonstrate presence or absence of protective effects towards liver cancer [100]. For daily clinical management of patients with diabetes mellitus and liver disease it is of particular importance to appreciate that metformin does not exacerbate nor cause liver injury and therefore no dose adjustments are needed in the presence of hepatic impairment [101, 102]. However, development of lactic acidosis can occur when using metformin in patients with advanced liver cirrhosis in whom renal impairment is not uncommon [103].

Thiazolidinediones (TZDs) is another class of oral hypoglycemic agents that serve as insulin sensitizers. As selective agonists for peroxisome proliferator-activated receptor γ, TZDs such as pioglitazone improve insulin sensitivity at the level of adipose tissue, liver and muscle by protecting non-adipose tissues against lipid overload, balancing the secretion of adipocytokines and inhibition of lipolysis [104, 105]. By improving insulin sensitivity, TZDS may even delay the onset of diabetes mellitus in patients with impaired glucose tolerance [106]. Several clinical trials investigated the effects of TZDs in patients with NAFLD [107]. The largest one using pioglitazone enrolled non-diabetic patients with biopsy-proven NASH [108] and demonstrated improvements in steatosis, liver enzymes and inflammation. Interestingly a greater proportion of patients on pioglitazone had an entirely resolution of steatohepatitis on liver biopsy at the end of treatment. Identification of predictors of response will be crucial along with studies to assess long-term benefits, particularly since the beneficial effects appear to be short-lived after halting treatment [109]. Weight gain of up to 6kg within the first 12 months of treatment is almost universal [110] and may represent either adipose tissue expansion or water retention. Since long-term use of TZDs is possibly linked to congestive heart failure, reduced bone mineral density with fractures and increased incidence of bladder cancer [111], risks and benefits must be carefully weighted and patients monitored once treatment has been initiated. At least the increased risk for bladder cancer was not confirmed in a recent global study involving six cohorts of diabetic patients [112].

By targeting the nuclear farnesoid X receptor (FXR), bile acids have been shown to not only be detergent-like molecules but also key signaling molecules involved in pathways that regulate bile acid, lipid and glucose metabolism [113]. Activation of FXR has also anti-inflammatory and anti-fibrotic effects, respectively [114]. By improving insulin sensitivity, FXR agonists such as obeticholic acid (OCA), a 6α-ethyl derivative of chenodeocxcholic acid, may represent promising drugs particularly for the treatment of diabetic patients with NAFLD [115, 116]. When given to patients with diabetes mellitus and NAFLD in a placebo-controlled trial [117], OCA indeed increased insulin sensitivity and also resulted in a decrease in body weight. The effect of OCA has been further explored in a large number of non-cirrhotic patients with biopsy-proven NASH [118]. This placebo-controlled FLINT trial was stopped early due to OCA mediated improvement in liver histology. Studies are ongoing to explore the anti-inflammatory and anti-fibrotic effects of OCA as well as potential cardiovascular consequences of an increase in low density lipoprotein cholesterol observed in the FLINT trial.

Peroxisome proliferator-activated receptors (PPARs) are fatty

acid-activated receptors [119]. While single PPARα agonists like fibrates do not appear to be beneficial in patients with NAFLD [120], the dual PPARα/δ agonist GFT505 has recently been shown to be liver protective with regard to steatosis, inflammation and fibrosis in a PPAR-dependent and -independent fashion [121]. GFT505 has also been shown to improve insulin sensitivity, dyslipidemia and elevated liver enzymes in obese patients with dyslipidemia or impaired glucose metabolism [122]. Of note, GFT505 exhibited antifibrotic effects independent of insulin resistance and metabolic abnormalities [121]. These findings prompted a placebo controlled study in patients with biopsy-proven NASH that aims at demonstrating reversal of NASH without worsening of fibrosis.

Lipid-lowering agents

Cardiovascular disease resulting from dyslipidemia is the major cause of morbidity and mortality for individuals with diabetes mellitus. Therefore it is not surprising that patients are often treated with statins to minimize cardiovascular mortality. A substantial number of patients receiving statin treatment for cardiovascular protection have coexisting NAFLD and that on its own is known for fluctuating liver enzymes [17]. Therefore liver enzyme elevations during statin therapy do not necessarily reflect drug-induced liver injury. Statin toxicity is very low and the US Food and Drug Administration followed recommendations of a liver expert panel [123] and dropped the requirement of liver enzyme monitoring during statin therapy. More recently clinical trials and meta-analyses have shown that statin therapy appears to be associated with new-onset diabetes mellitus. As cardiovascular benefits of statins outweigh this risk, no change in clinical practice is currently recommended [124]. The effects of statins on liver histology are limited and thus statins do not have a role in reversing NASH or preventing progression of NAFLD. Unless proven otherwise, the sole indication for statins in NAFLD is treatment of dyslipidemia [59]. Considering NAFLD being independently associated with an increased cardiovascular risk, statin efficacy in patients with NAFLD may need to be measured as reduction in cardiovascular events, rather than improvement in liver histology [125] and likely outweigh the current lack of specific histologic improvement.

Outlook

Over the last twenty-five years since its initial description, tremendous progress has been made in our understanding of nonalcoholic fatty liver disease. Several challenges however remain and include the need to develop more precise tools that allow us to identify patients with and without diabetes mellitus that are at particular risk to develop steatohepatitis and potentially progress to liver cirrhosis. Hepatocellular carcinoma does occur in non-cirrhotic patients and therefore it will be of clinical importance to identify those individuals at minimal risk to allow for cost-effective screening efforts. Albeit liver histology likely will remain part of the work-up for another couple of years and be an important component to assess efficacy of new drugs under development, future research needs to explore improved methods of noninvasive monitoring of disease activity. New pharmacological agents currently under development for diabetes mellitus may also be efficacious for the treatment of NAFLD, but drug development targeting different pathways in the disease pathogenesis also represents an unmet need. Expectations from patients for prescription NAFLD drugs are high and have overcome the current need for a liver biopsy needed for recruitment into large placebo-controlled trials. The future looks bright.

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