Published in final edited form as:

Am J Gastroenterol. 2010 July ; 105(7): 1567–1573. doi:10.1038/ajg.2010.18.

NONALCOHOLIC FATTY LIVER DISEASE INCREASES RISK OF DEATH AMONG PATIENTS WITH DIABETES: A COMMUNITY-BASED COHORT STUDY

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Abstract

Introduction—The significance of non-alcoholic fatty liver disease (NAFLD) among patients with diabetes is unknown. We sought to determine whether a diagnosis of NAFLD influenced mortality among a community-based cohort of patients with type 2 diabetes mellitus.

Methods—337 residents of Olmsted County, Minnesota with diabetes mellitus diagnosed between 1980–2000 were identified using the Rochester Epidemiology Project and the Mayo Laboratory

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Conflict of Interest Items

a. Which author is the guarantor of the manuscript?

Leon Adams

b. What was each author's contribution to the paper?

Leon Adams contributed to study design, data collection and analysis and interpretation and manuscript writing.

Scott Harmsen, Jennifer L. St.Sauver and Felicity B. Enders all contributed to the study design, data analysis and interpretation.

Terry Therneau contributed to the data analysis and interpretation.

Phunchai Charatcharoenwittaya contributed to the data collection and manuscript preparation.

Paul Angulo contributed to study design, data analysis and interpretation and manuscript writing.

c. What financial support was given to the project?

The study was supported by an R01 DK82426 to Dr Paul Angulo. Dr Leon Adams was sponsored by medical research scholarships from the National Health and Medical Research Council (No. 353710) and The University of Western Australia (Athelstan and Amy Saw Scholarship).

d. What potential competing interests exist?

None.

Information System and followed for 10.9 ± 5.2 years (range 0.1–25). Survival was analysed using Cox proportional hazards modelling with NAFLD treated as a time-dependent covariate.

Results—Among the 337 residents, 116 were diagnosed with NAFLD 0.9 ± 4.6 years after diabetes diagnosis. Patients with NAFLD were younger, and more likely to be female, and obese. Overall 99/337 (29%) patients died. In multivariate analysis to adjust for confounders, overall mortality was significantly associated with a diagnosis of NAFLD (hazard ratio [HR] 2.2; 95% confidence Interval [CI] 1.1, 4.2; $p = 0.03$), presence of ischemic heart disease (HR 2.3; 95% CI 1.2, 4.4), and duration of diabetes (HR per 1 year, 1.1; 95% CI 1.03, 1.2). The most common causes of death in the NAFLD cohort were malignancy (33% of deaths), liver-related complications (19% of deaths), and ischemic heart disease (19% of deaths). In adjusted multivariate models, NAFLD was borderline associated with an increased risk of dying from malignancy (HR 2.3; 95% CI 0.9, 5.9; $p = 0.09$), and not from cardiovascular disease (HR 0.9; 95% CI 0.3, 2.4; $p = 0.81$)

Conclusions—The diagnosis of NAFLD is associated with an increased risk of overall death among patients with diabetes mellitus.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common diagnosis in clinical practice of several medical specialties.¹ In the United States, 1 in 3 adults and 1 in 10 children or adolescents suffer from NAFLD.^{2–3} Similarly, the prevalence of diabetes mellitus has reached proportions never observed before, with 8% of individuals in the United States affected with the disease.⁴ In addition, it has recently been estimated that people born in the year 2000 have a 33–38% lifetime risk of developing diabetes.⁵

The pathogenesis of diabetes and NAFLD are intimately related to insulin resistance and hyperinsulinemia.⁶ Consequently, diabetes mellitus is frequently observed in patients with NAFLD, being present in 18–45% of cases.^{3, 7–8} Similarly, NAFLD is common among patients with type 2 diabetes with the prevalence ranging between 49–75%.^{9–11}

Concomitant diabetes mellitus among patients with NAFLD is associated with more severe inflammation and fibrosis on liver biopsy and with a more rapid fibrosis progression.^{12–14} In addition, diabetes is recognized to increase the risk of cirrhosis related complications such as hepatocellular carcinoma.¹⁵ Furthermore, the presence of diabetes mellitus increases the risk for liver related death and overall death among patients with NAFLD.^{8, 16} Direct up-regulation of fibrogenic growth factors by hyperinsulinemia and hyperglycemia¹⁷ along with changes in adipocytokine levels which accompany diabetes such as increased tumor necrosis factor alpha and reduced adiponectin levels¹⁸ may play significant roles in contributing to liver damage and development of complications in NAFLD patients who suffer from diabetes.

Although it is clear that diabetes mellitus is of prognostic significance among patients with NAFLD^{8, 10, 14, 16} it is not clear whether NAFLD is of prognostic significance among patients with diabetes mellitus. In a large community-based study we have recently demonstrated that NAFLD is independently associated with an increased risk of all-cause mortality compared to the general population of the same age and gender.¹⁶ This higher mortality among patients with NAFLD was subsequently confirmed in a Swedish study of patients presenting with elevated liver enzymes due to NAFLD.¹⁹ The prevalence of diabetes mellitus in the Swedish study was 37.5%; the prevalence of diabetes in our community cohort with NAFLD was 26% as compared to a prevalence of 5% in the same community population.²⁰ The comparative control group in both series was matched only by age and gender to the NAFLD cases^{16, 19}, and thus, it remains uncertain whether the higher mortality in the NAFLD group in both studies was because of this higher prevalence of diabetes, or NAFLD itself. We therefore performed a longitudinal community-based cohort study of subjects with diabetes mellitus to examine

whether the presence of NAFLD is associated with an increased risk of overall mortality, and cause-specific mortality, compared to a control group who had been tested for liver abnormalities but were negative for NAFLD.

METHODS

The study was approved by the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center, and all participants provided permission for their medical records to be used for research.

Study Setting

The study population was derived from residents of Olmsted County located in southeastern Minnesota. Population-based epidemiological research can be conducted in Olmsted County, Minnesota, because medical care is virtually self-contained within the community and there are only few health care providers. Each of these providers utilizes a unit medical record whereby all inpatient and outpatient medical information for patients is accumulated in a single record. All diagnoses made in outpatient office or clinic visits, hospitalizations, emergency room visits, nursing home care, surgical procedures, autopsies, and death certificates are indexed and retrievable through the Rochester Epidemiology Project (REP).^{21–22} Each year, 87% of Olmsted County residents are seen at least once by a health care professional and, in any given 4-year period, at least 1 health encounter is recorded in over 95% of county residents.²² Thus, the REP makes it possible to identify patients with certain characteristics (such as diabetes) and follow them longitudinally assessing long term outcomes such as mortality and causes of death.

Data Ascertainment

Patients with diabetes mellitus were identified using the resources of the REP and the Mayo Clinic Laboratory Information System (MLIS). The MLIS is a database of all blood test results performed by the Mayo Clinic Laboratories since 1983. The database includes information on the geographical residence of patients allowing categorization of blood results by County.

Patients with diabetes mellitus were identified by firstly searching the REP master diagnostic index using Hospital Adaptation of International Classification of Diseases (HICDA) codes for diabetes and its complications (250.0110-8, 250.2110-5, 250.2210, 250.2310, 250.2410, 250.2420, 250.2510, 250.2610, 250.2611-4, 250.6110-5, 377.4410, 377.4420, 445.9120, 707.9180, 374.8210, 537.9670, 782.1120, 962.3110, 962.3211). Secondly, as the diagnostic criteria for diabetes have changed over the past two decades, the MLIS database was searched for all Olmsted County residents with an outpatient fasting blood glucose (FBG) level ≥ 126 mg/dl to ensure as complete ascertainment as possible. Patients with a concomitant diagnosis of NAFLD were identified using HICDA codes for fatty liver, hepatic steatosis or steatohepatitis (5710-42-42, 5710-43-1, 5710-43-0, 5470-42-0 to 4, 2790-44-1). From the cohort of patients identified as having diabetes, but not concomitant NAFLD, a random 9.5% sample subset of 684 patients were selected after stratification by time period of diagnosis (1980–85, 1986–90, 1991–95, 1996–1999) to ensure similar periods of follow-up as the NAFLD patients. Medical records of patients identified were extensively reviewed to ensure patients fulfilled the case definitions (see below).

Diabetes case ascertainment was over a 20 year period from January 1st 1980 to December 31st 1999. As we wished to examine whether a diagnosis of NAFLD was a risk factor for mortality among patients with diabetes mellitus, we included patients diagnosed with diabetes for the first time on or after January 1st 1980. The year 1980 was chosen, as NAFLD was better

defined as a disease entity in this year.²³ The date 12/31/1999 was chosen to allow a 20-year ascertainment period. Patient follow-up was extended up to January 1st 2005.

Case Definitions

The diagnosis of diabetes required a fasting blood glucose level ≥ 126 mg/dl or a random glucose ≥ 200 mg/dl in presence of symptoms as recommended by the American Diabetes Association.²⁴ Date of diagnosis was from date of the first elevated fasting glucose level leading to the diagnosis of diabetes. Patients were excluded if they had type one diabetes or secondary causes for hyperglycemia (non-fasting, glucocorticoids, acute illness, Cushing's disease).

The diagnosis of NAFLD required confirmation of hepatic steatosis by either abdominal imaging (ultrasound, computed tomography or magnetic resonance imaging) or by liver biopsy. Patients with secondary causes for hepatic steatosis were excluded, as were patients with evidence of other liver disease on clinical history or examination, laboratory studies, imaging or biopsy. Patients at risk of viral hepatitis due to intravenous drug use or blood product transfusion prior to 1992, were excluded if they had not had hepatitis B or C serology performed after their exposure. Information on alcohol consumption (type, amount, frequency, duration as well as alcohol abuse screening questions) was collected prospectively as part of the medical record, by a patient history form filled out by the patient and reviewed by a nurse and physician at each visit. Patients with a daily ethanol consumption >20 grams were excluded.

Patients with diabetes but not NAFLD were required to have 1) a minimum of three sets of normal liver enzymes (alanine aminotransferase [ALT] <29 IU/ml for females, <45 IU/ml for males, aspartate aminotransferase [AST] <31 IU/ml for males and females, bilirubin <1.3 mg/dl, albumin <3.5 gm/l, alkaline phosphatase less than age and gender specific ranges of the MLIS); 2) normal liver enzymes at time of diabetes diagnosis and at any time measured during follow-up; and 3) absence of steatosis in imaging, if abdominal imaging studies were performed for any indication.

A total of 7,171 diabetics without NAFLD were identified from HICDA coding and the MILS over the study time period (1980–1999). From these subjects, a subset of 684 patients were randomly selected after stratification by time period of diagnosis and their medical records extensively reviewed to verify whether they fulfilled inclusion criteria. Reasons for exclusion from the study were: date of diagnosis of diabetes pre-1980 ($n=66$), type 1 diabetes ($n=41$), gestational diabetes ($n=6$), hyperglycemia due to medications or illness ($n=15$), hyperglycemia not within diabetic range ($n=36$), non-NAFLD liver disease ($n=9$), initial diabetes diagnosis outside of Olmsted County or non-County residents ($n=53$), unexplained elevated liver tests ($n=109$), less than three sets of liver enzymes measured ($n=45$) or evidence of hepatic steatosis on imaging after 1999 or at post-mortem ($n=83$). These exclusions left a total of 221/684 (32%) patients who fulfilled the inclusion criteria for diabetics without NAFLD. Extending this proportion to the 7171 subjects identified by HICDA coding and the MLIS as having diabetes without NAFLD, would mean approximately 2295 (32%) would fulfill our study criteria as having confirmed type 2 diabetes mellitus diagnosed in Olmsted County between 1980–1999 in the absence of NAFLD or other liver disease. One hundred and sixteen individuals fulfilling the same inclusion criteria for diagnosis of diabetes, geographical location and time period were identified as having concomitant NAFLD by HICDA coding. Three subjects were previously excluded due to diabetes being diagnosed after 1999.

Thus 337 subjects with type 2 diabetes (221 without NAFLD and 116 with NAFLD) comprised our study population. These 337 patients underwent a mean ($\pm$ SD) follow-up of 10.5 ($\pm$ 5.2) years (range 0.1–25 years). Of them, 116 patients were diagnosed with NAFLD 0.9 ($\pm$ 4.6) years (range of -9.9 to 16.1 years) after their initial diagnosis of diabetes mellitus. The other

221 patients with type 2 diabetes mellitus who did not develop NAFLD constitute the control group.

Data Abstraction

The following information was abstracted from the medical records at date of diagnosis of diabetes; age, gender, race, diabetes treatment required within three months of diagnosis, past medical history of hyperlipidemia, hypertension, ischemic heart disease, cerebrovascular disease, chronic renal failure, height, weight, blood pressure, medications, laboratory data (bilirubin, AST, ALT, alkaline phosphatase, albumin, fasting glucose, glycosylated hemoglobin, total cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride level). In addition, for patients with diabetes but not NAFLD, serial liver tests after time of diagnosis of diabetes and any hepatic imaging studies were recorded. Follow-up and cause of death were obtained from medical records and death certificates.

Statistical Analysis

The results are presented as number and percent or as mean and standard deviation. Baseline characteristics of patients with or without NAFLD are compared using student's t test, Chi squared tables or Fishers exact test when appropriate. Cox proportional hazards modeling was used to evaluate overall mortality. Co-morbidities diagnosed at time of diabetes diagnosis were entered into separate cox proportional hazard models after adjustment for age, gender and date of diabetes diagnosis (duration of diabetes). NAFLD was treated as a time dependent covariate from date of diabetes diagnosis. To assess the independent effect of NAFLD on mortality, variables that were considered to be potential confounders were entered into a multivariable Cox proportional hazard model. Two way interactions between NAFLD and age, gender, date of diabetes diagnosis respectively, as well as age and gender were performed with no significant interaction found at the $\alpha = 0.05$ level. Analysis was performed using SAS Release 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

Patients Characteristics

A total of 337 subjects with type 2 diabetes mellitus were identified; 116 had a confirmed diagnosis of NAFLD either prior to the diagnosis of diabetes or during follow-up, and 221 were without a diagnosis of NAFLD. Subjects without NAFLD were significantly more likely to be male, older and ex or current smokers, compared to those who developed NAFLD (Table 1). Subjects with NAFLD were more likely to be obese and correspondingly had a higher mean body mass index. There was no significant difference in prevalence of other features of the metabolic syndrome including hypertension, hypertriglyceridemia, or low-HDL cholesterol levels. Also, the prevalence of ischemic heart disease or cerebrovascular disease either alone or in combination was not significantly different between the two groups. Similarly, there was no difference in the apparent severity of diabetes with HbA1c values similar between the two groups. Further, the treatment regimens for diabetes and use of medication for hypertension and hyperlipidemia were similar between the two groups.

Of the 116 diabetic subjects diagnosed with NAFLD, 114 underwent abdominal imaging studies (85 ultrasound and 29 computed tomography) and 26 had a liver biopsy performed. As expected, subjects with NAFLD had higher levels of ALT and AST at time of diagnosis of diabetes compared to those without NAFLD.

Follow-up

The mean ($\pm$ standard deviation) duration of follow-up of the total cohort from time of diagnosis of diabetes was 10.9 ($\pm$ 5.2) years with a range of 0.1–25.0 years. The diagnosis of NAFLD followed the initial diagnosis of diabetes after a mean of 0.9 ($\pm$ 4.6) years with a range of –9.9 to 16.1 years in the 116 subjects. The average follow-up from initial diagnosis of diabetes was shorter among subjects who developed NAFLD than those that did not (9.2 ± 5.2 years vs. 11.7 ± 5.0 years, $p < 0.001$) due to higher mortality rate in the NAFLD group.

Causes of death

Overall, 99 (29%) subjects died during follow-up; 27 with NAFLD and 72 without NAFLD (Table 2). The most common causes of death were malignancy in patients with NAFLD, and ischemic heart disease in patients without NAFLD. Both malignancy and ischemic heart disease accounted for over half of all deaths in both groups. Among diabetic patients with NAFLD, liver complications and heart disease were the second leading causes of death, each accounting for 19% of all deaths in this group. Of the liver related deaths, one patient died from liver failure secondary to cirrhosis complicated by hepatocellular carcinoma; the other patients died from liver failure ($n=3$) and variceal bleeding ($n=1$). No liver related deaths were seen in the group without NAFLD.

The Impact of NAFLD on Mortality

The effect of NAFLD and other co-morbidities upon mortality among patients with diabetes mellitus, were examined in separate Cox proportional hazards models after adjustment for age, gender, and date of diagnosis of diabetes (i.e., duration of follow-up) (table 3). NAFLD was significantly associated with an increased risk of death (hazard ratio 1.7, 95% confidence interval 1.04–2.7). Means of diagnosis for NAFLD was associated with a difference in mortality with those who underwent liver biopsy having a higher risk of death ($p < 0.001$) with a hazard ratio of 5.3 (95% CI 2.4–11.5) which remained virtually unchanged after adjustment for age, gender and date of diabetes diagnosis (HR=5.3, 95% CI, 2.2–12.9, $p < 0.001$). No patient died from biopsy related complications. In addition, a history of ischemic heart disease or cerebrovascular disease were also associated with an increased risk of death.

To assess whether NAFLD was independently associated with an increased risk of all cause mortality, potential confounders were entered into a multi-variable Cox proportional hazard model (Table 4). NAFLD remained an independent risk factor for mortality when controlling for all other potential confounders. Age, duration of diabetes, prior malignancy, cerebrovascular disease, and ischemic heart disease were also independently associated with risk of death. Treatment regimens for diabetes (oral hypoglycaemic or insulin), or the use of medications for hyperlipidemia or hypertension did not affect mortality and did not change the significance of the association of NAFLD with mortality.

To determine whether patients with NAFLD had a greater risk of a specific cause of death, multivariable Cox proportional hazards modelling was used with the end-points of death due to heart disease, cardiovascular disease (combination of death from ischemic heart disease and cerebrovascular disease), malignancy and liver related death. After adjustment for age, gender, obesity and date of diabetes diagnosis, patients with NAFLD were at a borderline significantly greater risk of death from malignancy (HR 2.3, 95% CI 0.9–5.9, $p=0.09$). There was no increase in risk of death from heart disease (HR 1.1, 95% CI 0.4–3.1, $p=0.89$) or cardiovascular (i.e., heart plus cerebrovascular) disease (HR 0.9, 95% CI 0.3–2.4, $p=0.81$). The hazard ratio for liver related death was not able to be calculated as no subjects without NAFLD died from liver related causes.

DISCUSSION

As NAFLD is common and generally asymptomatic in patients with diabetes mellitus, the clinical significance of NAFLD has traditionally been overlooked. In this study, we have shown that presence of NAFLD is associated with an increased overall mortality, and a significantly higher mortality due to liver disease and malignancy in patients with type 2 diabetes. Importantly, this association is independent of classical risk factors and several features of the metabolic syndrome. Subjects with diabetes but not NAFLD were significantly older and had a longer period of follow-up potentially favouring an increased risk of death in this group. However, after adjustment for potential confounding variables, patients with diabetes and NAFLD had a 2.4 fold higher risk of dying as compared to patients with diabetes without NAFLD. Furthermore, the presence of NAFLD was associated with a higher risk of death than a past history of ischemic heart disease.

Liver related death accounted for 19% of all deaths of patients with NAFLD and diabetes whereas no subjects without NAFLD died from liver related causes. This suggests NAFLD may be directly responsible for a proportion of the increased risk of overall death by leading to cirrhosis with fatal complications of HCC, liver failure and variceal bleeding. Supporting this is evidence from the Verona Diabetes Study which found the risk of death from cirrhosis among diabetics is higher than that of the general population (standardized mortality ratio or SMR = 2.5) which is greater than the risk of death from cardiovascular complications (SMR = 1.34).²⁵

Subjects undergoing liver biopsy had a greater hazard ratio for death, although this was unaffected by age, gender or date of diabetes diagnosis. This highlights the selection bias of non-community based natural history studies which rely on biopsy and the difficulty in generalizing results from patients who have undergone liver biopsy to subjects diagnosed in the community. Patients undergoing biopsy are more likely to have significant liver disease and thus have a higher risk of liver related death. Subsequently these cohorts will over-estimate mortality rates when applied to the general community.

Patients with NAFLD were also had a trend towards a greater risk of dying from malignancy compared to subjects without NAFLD. A Danish population-based study found an increased risk of hepatic and non-hepatic related malignancy among 1800 subjects discharged from hospital with a diagnosis of NAFLD compared to the general population.⁵ The potential mechanisms through which NAFLD may lead to an increased risk of malignancy are unclear. NAFLD associated cirrhosis may be complicated by HCC and this occurred in one patient, although this patient was included among the liver related deaths rather than deaths secondary to malignancy. Subjects with NAFLD were significantly heavier and had a higher prevalence of obesity than subjects without NAFLD. Obesity is an established risk factor for a range of malignancies.²⁶ In addition, hepatic steatosis increases hepatic insulin resistance and may exacerbate hyperinsulinemia.^{27–28} In vitro studies have demonstrated that insulin is mitogenic to colonic mucosa²⁹ and hyperinsulinemia has recently been identified as an independent risk factor for colorectal malignancy at a population level.³⁰ Subsequently, the metabolic features associated with NAFLD may have increased the risk of malignancy in our cohort.

One of the strengths of the study is that it is community based and thereby minimizes the potential for selection bias and increases the ability to generalize the results to the general population. Ascertainment was maximized by using two sources to identify potential patients – the REP and the MLIS. In addition, the REP allows evaluation of prospectively collected data and permits a long period of follow-up. Inherent in any medical record based review is the potential for the clinician to not record or miss the diagnosis of NAFLD. We minimized this potential by also examining all biochemical results over time with at least three liver

enzymes sets determined in every patient. Although it is well recognized that liver enzymes may be normal among patients with NAFLD,³¹ it is also well known that liver enzymes fluctuate over time among subjects with NAFLD³² and thus the chance of misclassifying an undiagnosed patient with NAFLD is minimized by taking into consideration several liver enzyme measurements. Further, any potential misclassification of NAFLD subjects as non-NAFLD subjects would weaken any association in favour of no difference; therefore, the association we found is more likely to be real. It is possible that some subjects were falsely diagnosed with fatty liver, however as ultrasound has a high (>90%) sensitivity and specificity for the detection of fatty liver, and as the diagnosis required clinical confirmation by the managing physician, we feel this is unlikely.³³

Recently, Targher et al. have reported that 35.1% of patients with type 2 diabetes seen in a single tertiary care medical center in Italy suffered from cardiovascular disease as defined by the sum of coronary heart disease and cerebral and peripheral vascular disease.³⁴ This figure is higher than the 26.1% found in our community-based study. Similarly, 77% (1349/1749) of the total cohort of patients with type 2 diabetes in the Italian series³⁴ suffered from NAFLD as compared to 34.4% (116/337) in our series. In addition, the prevalence of several features of the metabolic syndrome was significantly higher among patients with NAFLD in the Italian series, but was not significantly different between patients with and without NAFLD in our series. All these differences between the two series can easily be explained by differences in study design leading to the inclusion of different patient populations. For instance, the Italian report³⁴ was a cross-sectional study with the prevalence of cardiovascular disease, NAFLD, and components of the metabolic syndrome determined at a single point in time after several years of suffering from diabetes, whereas the prevalence of all those conditions in our series was determined at the time of diabetes diagnosis. The cumulative incidence of cardiovascular disease and the components of the metabolic syndrome, and most likely the development of NAFLD as well, is expected to increase as the duration of diabetes lengthens. In this same cohort of diabetic patients, the Italian group recently reported that presence of NAFLD was associated with a 53% higher risk for the development of cardiovascular events within a five-year follow-up period.³⁵ However, over two thirds of the cardiovascular events recorded in that study were not fatal, and thus, the impact of NAFLD, if any, on cardiovascular-related deaths could not be estimated. Further, as other causes of death were not analysed, the impact of NAFLD on overall mortality could not be analysed. It is possible, however, that the cohort number in our study was not sufficient to detect small differences in cardiovascular death rates between NAFLD and non-NAFLD groups.

In summary, we found the diagnosis of NAFLD was an adverse prognostic indicator of all-cause death among patients with diabetes mellitus. Liver related death was responsible for a substantial proportion of deaths among patients with NAFLD. Therefore patients with diabetes should be evaluated for evidence of NAFLD and considered for therapy. Further research is required to assess whether treatment of NAFLD leads to a reduction in liver and overall mortality rates.

STUDY HIGHLIGHTS

1. WHAT IS CURRENT KNOWLEDGE.

- Nonalcoholic fatty liver disease (NAFLD) is common in patients with type 2 diabetes.
- The impact of NAFLD on morbidity and mortality in patients with diabetes is poorly described.

2. WHAT IS NEW HERE

- The presence of NAFLD is associated with an increased mortality rate in patients with type 2 diabetes.
- Excess mortality in patients with type 2 diabetes and NAFLD is in part attributable to increased liver related deaths.

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Table 1

Clinical characteristics at time of diagnosis of diabetes.

Variable	Total Cohort (n=337)	DM + NAFLD (n=116)	DM – NALFD (n=221)	P value
Age (years)	58 ± 13	55 ± 13	59 ± 13	0.005
Male	165 (49%)	43 (37%)	122 (55%)	0.002
BMI (kg/m ²)	32.7 ± 6.9	34.2 ± 7.5	31.9 ± 6.4	0.008
Obese (BMI ≥ 30 kg/m ²)	198/315 (64%)	77/110 (70%)	117/205 (57%)	0.02
Diabetes treatment: Diet/Oral/Insulin	233 / 82 / 22 (69% / 24% / 7%)	84 / 26 / 6 (72% / 22% / 5%)	149 / 56 / 16 (67% / 25% / 7%)	0.6
Hypertension (≥130/≥85)	213/334 (63%)	72/116 (62%)	141/218 (65%)	0.6
Hypertriglyceridemia ≥ 150 mg/dL	187/257 (73%)	70/88 (80%)	117/169 (69%)	0.08
Low HDL cholesterol ♀ ≤ 50 mg/dL ♂ ≤ 40 mg/dL	136/191 (71%)	56/73 (77%)	80/118 (68%)	0.2
Ischemic Heart Disease	55/334 (16%)	16/115 (14%)	39/219 (18%)	0.4
Cerebrovascular Disease	17/334 (5%)	5/115 (4%)	12/219 (5%)	0.7
Cardiovascular disease*	72/334 (21.6%)	21/115 (18.3%)	51/219 (23.3%)	0.3
Smoking Status Non / Ex / Current	193 / 76 / 65 58% / 23% / 19%	78 / 19 / 18 68% / 16% / 16%	115 / 57 / 47 53% / 26% / 21%	0.02
Bilirubin (mg/dL)	0.6 ± 0.4	0.7 ± 0.6	0.6 ± 0.4	0.4
ALT (IU/L)	33 ± 31	69 ± 42	28 ± 16	<0.001
AST (IU/L)	58 ± 41	54 ± 43	21 ± 5	<0.001
Albumin (gm/dl)	4.2 ± 0.4	4.2 ± 0.5	4.2 ± 0.3	0.9
HbA1c	10.3 ± 3.5	10.1 ± 3.7	10.4 ± 3.4	0.6
Triglyceride (mg/dl)	263 ± 207	300 ± 267	242 ± 164	0.07
HDL cholesterol (mg/dl)	44 ± 23	44 ± 26	43 ± 21	0.7

* Cardiovascular disease denotes cases of ischemic heart disease plus cases of cerebrovascular disease. Comparisons made using student's t test, Chi squared tables or Fishers exact test.

Table 2

Causes of Death

	Total Cohort (n=337)	DM + NAFLD (n=116)	DM – NAFLD (n=221)
Overall	99	27	72
Heart Disease	31 (31%)	5 (19%)	26 (36%)
Cerebrovascular	5 (5%)	0 (0%)	5 (7%)
Malignancy	23 (23%)	9 (33%)	13 (18%)
Infection	15 (15%)	3 (11%)	12 (17%)
Liver Related	5 (5%)	5 (19%)	0
Other	18 (18%)	4 (15%)	14 (20%)
Unknown	2 (2%)	1 (3%)	1 (2%)

Table 3

Univariate Cox proportional hazard modeling for predictors of mortality adjusted for age, gender and duration of diabetes

Variable	P value	H.R.	95% C.I.
Smoker	0.17	1.4	0.9–2.3
Hypertension	0.26	1.4	0.8–2.4
Obesity	0.33	0.8	0.5–1.3
Hyperlipidemia	0.71	0.9	0.4–1.9
Prior Malignancy	0.07	2.0	0.9–4.2
CVD	0.002	2.9	1.5–5.6
IHD	0.017	2.0	1.1–3.6
NAFLD	0.03	1.7	1.04–2.7

IHD = Ischemic Heart Disease, CVD=Cerebrovascular Disease. Hypertension defined as >135/85 or taking anti-hypertensive medication, Obesity defined as BMI ≥ 30 kg/m², Hyperlipidemia defined as elevated triglycerides (≥ 150 mg/dl), or low high density lipoprotein (HDL ≥ 40 mg/dl for men, ≥ 50 mg/dl for women) or taking lipid lowering medication.

Table 4

Multivariate Cox proportional hazard modelling for predictors of death in patients with diabetes mellitus

Variable	P value	H.R.	95% C.I.
Age <50		1.0 (reference)	
Age 50–60	0.22	2.2	0.6–7.9
Age 60–70	0.005	5.8	1.7–19.7
Age >70	<0.001	12.9	3.6–46.3
Gender	0.96	1.0	0.6–1.8
Date of DM diagnosis	0.01	1.1	1.03–1.2
Smoker	0.45	1.2	0.7–2.2
Hypertension	0.61	1.2	0.7–2.0
Obesity	0.65	0.9	0.5–1.5
Hyperlipidemia	0.14	0.5	0.2–1.3
Prior Malignancy	0.03	2.4	1.1–5.3
CVD	0.02	2.8	1.2–6.7
IHD	0.01	2.3	1.2–4.4
NAFLD	0.03	2.2	1.1–4.2

DM=diabetes mellitus, IHD = Ischemic Heart Disease, CVD=Cerebrovascular Disease. Hypertension defined as >135/85 or taking anti-hypertensive medication, Obesity defined as BMI ≥ 30 kg/m², Hyperlipidemia defined as elevated triglycerides (≥ 150 mg/dl), or low high density lipoprotein (HDL ≥ 40 mg/dl for men, ≥ 50 mg/dl for women) or taking lipid lowering medication.