LIVER

Mortality From Chronic Liver Diseases in Diabetes

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OBJECTIVES: **Mortality from chronic liver diseases (CLDs) is increased in diabetes, but little is known about the etiology. The aim of this study was to assess mortality rates from CLD by etiology in known diabetic subjects living in the Veneto Region, Northern Italy.**

METHODS: **A total of 167,621 diabetic subjects, aged 30–89 years (54.6% men), were identified in the year 2007 and their vital status was assessed between 2008 and 2010. Standardized mortality ratios (SMR) with 95% confidence intervals (CIs) were computed with regional mortality rates as reference. The underlying cause of death and all comordidities reported on the certificate were scrutinized in order to identify CLD deaths and their main etiologies. The latter were grouped into the following three categories: (i) virus-related, (ii) alcohol-related, and (iii) non-virus, non-alcohol-related (mainly represented by nonalcoholic fatty liver disease, NAFLD).**

RESULTS: **Analyses were based upon 473,374 person-years of follow-up and 17,134 deaths. We observed an increased risk of dying from CLD in diabetic subjects with an SMR of 2.47 (95% CI = 2.19–2.78) in men and 2.70 (2.24–3.23) in women. SMRs were 2.17 (1.90–2.47), 2.25 (1.98–2.54), and 2.86 (2.65–3.08) for virus-related, alcohol-related, and non-virus, non-alcohol-related CLD, respectively.**

CONCLUSIONS: **Diabetic patients have a twofold to threefold higher risk of dying of CLD, mainly associated with a non-virus and non-alcohol-related etiology, which is largely attributable to NAFLD. An early diagnosis and treatment of NAFLD, if any, may have a beneficial clinical impact on the survival of diabetic patients.**

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INTRODUCTION

Diabetes reduces lifetime by about 6 years, compared with that of subjects without diabetes (1), because it increases the risks of death from all causes, including chronic liver diseases (CLDs) (2–4). A ~2.5-fold higher risk of death from CLD was observed in a cohort study on 7,148 type 2 diabetes patients (5) as well as in a recent large study on more than one million subjects (6). It is known that CLD occurs due to different etiologies, such as alcohol and drug use, and viral, autoimmune, and metabolic causes. Nonalcoholic fatty liver disease (NAFLD), the most common cause of CLD among adults with or without type 2 diabetes in Western countries, has emerged as a public health problem of epidemic proportions worldwide (7–9). Notably, patients with type 2 diabetes and NAFLD are also more likely to develop the more advanced forms of NAFLD, such as nonalcoholic steatohepatitis, advanced fibrosis, cirrhosis, and, in some cases, hepatocellular carcinoma (7). In recent years, NAFLD has been recognized as a major risk factor of morbidity and mortality in type 2 diabetes (10,11). It is noteworthy that the prevalence of NAFLD is increasing and keeping pace with the steady worldwide growth of obesity, type 2 diabetes, and the metabolic syndrome (12). However, although it is known that mortality from CLD is increased in subjects with diabetes, to our knowledge, no information is currently available about the etiology of CLD-related deaths in this patient population.

In fact, mortality statistics are generally limited to the underlying cause of death. However, comorbidities are mentioned in death certificates and they might be used to provide a more comprehensive assessment of diseases that may contribute, more or less directly, to death. The analysis of all diseases reported on death certificates (multiple cause of death analysis) permits more extensive capture of CLD-related deaths, and allows the retrieval of the etiology of CLD. Although suffering from the underreporting of causes and types of liver diseases, the analysis of multiple causes of death data has been applied in US studies to assess the burden of hepatitis C virus (HCV) infection- and alcohol-related CLD in the overall population and in high-risk subgroups (13). The main

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aim of our study was to analyze all information available in death certificates in an entire region in Italy to investigate the etiology of CLD-associated mortality in diabetes.

METHODS

Identification and follow-up of a cohort of diabetic subjects

The Veneto Region (North-Eastern Italy) has about 4.9 million inhabitants; life expectancy is about 80 and 85 years in males and females, respectively, with circulatory diseases and cancer being the main causes of death. Hospital care is free of charge, although patients must contribute to out-of-hospital care and drug costs, unless they are affected by major chronic diseases, such as diabetes. Upon certification from a specialist, subjects with diabetes receive disease-specific care without any contribution to the costs. These subjects are listed in a regional electronic archive, which is a precious source for the identification of subjects affected by diabetes. This archive is estimated to include about 80% of subjects identified as diabetic by multiple data sources; in a previous survey in the Veneto Region, its positive predictive value was 98% for the diagnosis of diabetes in a sample of subjects aged 18–65 years (14). Although the date of diabetes diagnosis was not available, the archive included the date of diabetes registration in electronic records: such dates could correspond to the development of the electronic archive mainly in 1999–2000 and therefore could follow the diagnosis by several years, but allowed the identification of a sub-cohort of patients (those registered before 2001) who surely had at least 7 years of diabetes duration at the beginning of the follow-up.

In the Veneto Region, all death certificates are collected by the Local Health Units of the National Health Service and a copy of these is transmitted to the Regional Epidemiology Service. For the purpose of the present study, we identified in the electronic archive of the Veneto Region a cohort of diabetic patients aged 30–89 years who were exempt from medical charges for diabetes treatment in December 2007, and linked them with the electronic archive of causes of deaths that occurred in the period from 2008 to 2010. The record-linkage was performed on previously anonymized records, without any possibility of identification of individuals. The informed consent requirement for this study was exempted by the ethics committee because researchers only accessed retrospectively a de-identified database for analysis purposes. Each subject was followed from 1 January 2008 either until death, or 90 years of age, or 31 December 2010, whichever came first.

Analysis of multiple causes of death

As previously mentioned, a copy of the death certificates of all residents in the Veneto Region is centrally transmitted to the Regional Epidemiology Service for coding of causes of death according to the International Classification of Diseases, 10th Edition. Since 2008, the electronic regional archive of mortality includes not only the underlying cause of death but also all diseases mentioned in the death certificate, both in part I (i.e., conditions involved in the causal chain of events leading to death) and in part II (i.e., other significant conditions contributing to death).

To identify CLD-related deaths, codes usually adopted in liver cirrhosis mortality statistics (K70, K73, K74) were selected in any position of the death certificate. The disease was further classified as being related to viral hepatitis infection (codes, B15-B19), to alcohol (codes for alcoholic liver diseases and for mental and behavioral disorders due to use of alcohol, K70 and F10), or to a non-viral non-alcohol-related etiology (NVNA-CLD).

Statistical analysis

Age-standardized mortality rates, using the direct method (European standard population), were computed among diabetics and the whole regional population for circulatory and neoplastic diseases and for CLD. Standardized mortality ratios (SMRs) with 95% confidence intervals, based on the Poisson distribution, were computed as the ratios between deaths observed in the diabetic cohort, and those expected according to age- and gender-specific regional mortality rates. SMRs were computed for both total mortality and the single nosologic categories on the basis of the underlying cause of death. Specifically, for CLD (overall, virus-related, alcohol-related, or NVNA-related), SMRs were also computed on the basis of all comorbidities reported in the death certificates. SMRs were assessed both in the whole cohort of diabetic subjects, separately by gender and three classes of age (adults, <65 years; young–old, 65–74 years; and elderly, ≥75 years), and in the sub-cohort with a longer duration of disease at the beginning of the follow-up.

RESULTS

As detailed in **Figure 1**, 176,771 diabetic subjects were initially identified in December 2007 from the regional electronic archive of exemptions from medical charge of the Veneto Region. Out of them, 209 were excluded because of incomplete data and 1,302 because they died in the last weeks of the year. Out of the cohort of 173,260 patients with complete data and alive on 31 December 2007, final analyses were restricted to the 167,621 subjects aged 30–89 years at the beginning of the follow-up, corresponding to 5.0% of the total regional population of the same age band. Of the cohort subjects, 54.6% were men, 38.2% were aged 30–64 years, 32.6% were aged 65–74 years, and 29.2% were aged 75–89 years, respectively. There were 473,374 person-years of follow-up in the period from 2008 to 2010, and 17,134 (10.2%) deaths occurred.

The crude mortality rate was higher in men than in women and, as expected, increased progressively with aging, reaching a crude mortality rate of 76.6 per 1,000 subjects among those aged 75–89 years (**Table 1**).

The main causes of death were cardiovascular diseases and neoplasms accounting for 34.6% and 31.0% of all deaths, respectively. CLD accounted for 2.3% of total deaths, and they were responsible for about half (47.2%) of the mortality from digestive diseases. Notably, as shown in **Table 2**, the diabetic cohort had a significantly greater mortality risk than the general population, with an overall SMR of 1.49 (95% confidence interval = 1.46–1.52) in men and 1.53 (1.49–1.56) in women, respectively. The excess in mortality of diabetic subjects with respect to the general population was much

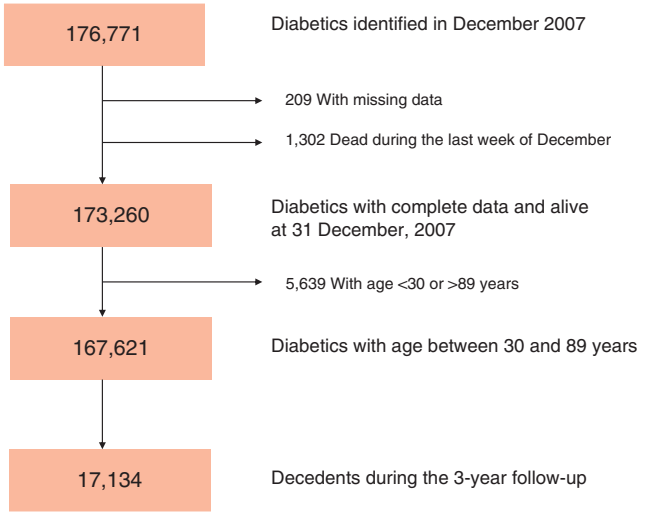

Figure 1. Schematic design of the enrollment and follow-up of the diabetic subjects.

Table 1. Person-years, number of deaths, and crude mortality rates stratified by sex and age classes of 167,621 diabetic subjects followed for 3 years

	Person-years	Number of deaths	Crude mortality rate × 1,000 subjects
Gender			
Men	258,912	9,866	38.1
Women	214,463	7,268	33.9
Age class (years)			
30–64	167,447	1,692	10.1
65–74	156,738	4,008	25.6
75–89	149,190	11,434	76.6

larger among younger age classes. All the main causes of death showed a significantly higher risk in diabetes (**Figure 2**, **Table 2**). The risk of dying from CLD was markedly increased among diabetic subjects with respect to the general population, with a SMR of 2.47 (2.19–2.78) for men and of 2.70 (2.24–3.23) for women.

When all diseases reported in death certificates were analyzed, CLD was mentioned as either a causing or a contributing factor in 6.9% of the total deaths that occurred in diabetic subjects. The 2.5-fold relative risk estimated by analyses restricted to the underlying cause of death was confirmed. Interestingly, as reported in **Table 3**, NVNA-related CLD, which represented about two-thirds of cases of all CLD-related deaths among diabetics, had a SMR of 2.86 (2.65–3.08), whereas SMRs for virus-related and alcohol-related CLD were 2.17 (1.90–2.47) and 2.25 (1.98–2.54), respectively. As shown in **Table 4**, when the analysis of mortality from CLD was stratified by sex and age, the SMRs for NVNA-related CLD remained the highest in all age classes and in both sexes. It is noteworthy that the SMR for NVNA-related CLD was higher in younger subjects (30–64 class of age) and decreased across the three classes of age. Also worth mentioning is that the SMR for NVNA-related CLD death was remarkably higher in women than in men.

Finally, when analyses were carried out in the sub-cohort with at least 7 years of diabetes duration, the estimated mortality risk for CLD only slightly decreased in the underlying cause of death analysis (SMR = 2.33, 1.99–2.71), and remained unchanged in the multiple causes analysis both for all CLD (SMR = 2.55, 2.34–2.77) and for NVNA-related CLD (SMR = 2.89, 2.59–3.22, data not shown).

DISCUSSION

We and others have reported an increased mortality from CLD in diabetes (5,6). The results of the present study confirm that diabetic persons have a two- to threefold increased risk of dying from CLD and, most importantly, point out that all main etiologies of CLD (e.g., virus, alcohol) contribute to this increased risk. However, the main result of our study is that the greater contribution to CLD mortality comes from NVNA-related CLD death, mainly represented by NAFLD. They also include rarer causes such as toxic substances (e.g., drugs), autoimmunity, and hemocromatosis.

It is well known that most subjects with CLD not attributable to prior virus infection or alcohol abuse have NAFLD (15). It is also well known that most subjects with type 2 diabetes have NAFLD (9,16). Therefore, it is reasonable to assume that the largest fraction of deaths we have coded as NVNA-related CLD were NAFLD-related. In fact, NAFLD is not a benign condition but encompasses a large spectrum of hepatic disorders including fatty liver, steatohepatitis, and liver cirrhosis (17), which confer an increased risk of dying not only from liver failure but also from cardiovascular disease and chronic kidney disease (7,9,18). When liver diseases reported in death certificates were carefully analyzed, we found that NVNA-related CLD was associated with higher SMRs than virus-related CLD or alcohol-related CLD (approximately three vs. two) and this result was observed in women more than in men and at all ages. These findings point out that prevention of liver disease should not target only viral infection or alcohol abuse by specific vaccination or educational campaigns but should also implement strategies aiming to reduce NAFLD. The latter should emphasize the need to avoid weight gain and to promote weight loss when necessary. It is well known, indeed, that fatty liver is strictly related to whole body fat excess, mainly in the visceral area (12).

Recent studies, mainly in the general population, reported that the presence of NAFLD carries an increased risk of overall mortality and of mortality related to cardiovascular disease and liver disease (19–24,25). In the Dionysos cohort, a study of the Italian general population, the average prevalence of NAFLD was 55%, with a 24.5% prevalence in normal weight subjects (body mass index < 25 kg/m^2) and of 91% in obese subjects (body mass index > 30 kg/m^2) (26). However, in Italy, the main reported causes of liver cirrhosis are HCV infection (51.1%) and alcohol consumption (12.4%), with other less represented etiologies being autoimmune hepatitis and primary biliary cirrhosis (2%), and the metabolic CLDs (2%) (27). Nonetheless, in Northern Italy the prevalence of HCV is lower and the proportion of CLD with an alcoholic etiology is higher than the national average (28). It must be remarked that the cirrhotic state is itself associated with an

Table 2. SMR of 167,621 diabetic patients followed-up for 3 years: analysis of the underlying cause of death

	Men		Women	
	n	SMR (CI)	*n*	SMR (CI)
All causes	9,866	1.49 (1.46–1.52)	7,268	1.53 (1.49–1.56)
All causes, 30–64 years	1,264	2.14 (2.03–2.27)	428	2.52 (2.28–2.77)
All causes, 65–74 years	2,881	1.69 (1.63–1.75)	1,127	1.82 (1.71–1.93)
All causes, 75–89 years	5,721	1.32 (1.29–1.36)	5,713	1.44 (1.40–1.48)
Cardiovascular diseases	3,206	1.47 (1.42–1.52)	2,674	1.46 (1.40–1.51)
Neoplasms	3,425	1.30 (1.26–1.34)	1,893	1.32 (1.26–1.38)
Diabetes	1,184	6.11 (5.77–6.47)	1,019	6.68 (6.28–7.10)
Respiratory diseases	511	1.14 (1.04–1.24)	314	1.21 (1.08–1.35)
Digestive diseases	471	1.86 (1.70–2.04)	373	1.76 (1.58–1.96)
Chronic liver diseases	278	2.47 (2.19–2.78)	120	2.70 (2.24–3.23)

CI, confidence interval; SMR, standardized mortality ratio.

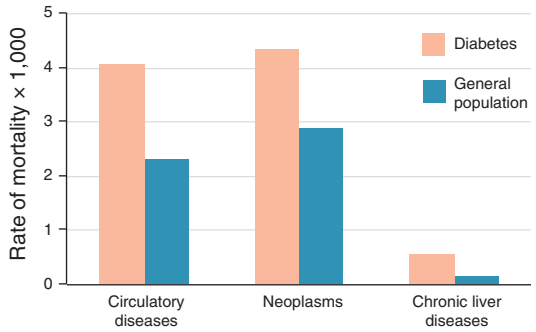

Figure 2. Age-standardized mortality rates (standard European population) for circulatory diseases, neoplasms, and chronic liver diseases among diabetics and the general population of the Veneto region aged 30–89 years.

Table 3. SMRs for CLDs reported as either the underlying or the contributing causes of death of 167,621 diabetic patients followed-up for 3 years

	Number of deaths	SMR	95% CIs
All CLD	1,183	2.55	2.41–2.70
Virus-related CLD[a]	234	2.17	1.90–2.47
Alcohol-related CLD[a]	260	2.25	1.98–2.54
NVNA-related CLD	707	2.86	2.65–3.08

CI, confidence interval; CLD, chronic liver disease; NVNA, non-viral non-alcohol; SMR, standardized mortality ratio.
[a]18 CLD deaths were classified as related to both alcohol and viral hepatitis.

increased risk of diabetes because of its impact on glucose metabolism; therefore, the increased mortality risk found for CLD in our study could be partly due to reverse causation (cirrhosis as a cause of diabetes). However, in spite of the rather short follow-up, we could identify a sub-cohort with long diabetes duration; in these subjects, the increased mortality risk found for CLD is less probable to be explained by diabetes developing from an advanced cirrhotic state.

Therefore, considering also that NAFLD and diabetes are a growing health problem (29–32), we believe that our results may have important clinical implications. Our study has a number of strengths, which include the great number of subjects evaluated, the completeness of information about vital status, the careful analysis of all aspects of death certificates (e.g., comorbidities). We are not aware of a study with these merits. The study, however, has some limitations. We totally lack data on diabetes type, treatment, and complications. However, here the point is to compare diabetic and nondiabetic subjects rather than to discuss about the impact on the results of clinical features of diabetes. The main limitation, in fact, is related to potential underreporting of data, which might be useful to better define the etiology of CLD, which was available in nearly half of the CLD deaths in the regional population, a figure similar to US studies (13). For example, alcohol-related CLD could be particularly affected by underreporting alcohol abuse due to prejudices associated to this misbehavior. Yet, excessive alcohol intake could be a feature of the remote past of the subjects who died and not of the years immediately preceding their death and, for such reason, may be erroneously not reported in the death certificate. Again, viral hepatitis might have occurred several years before death and, for such reason, may not be reported in the death certificate. However, such underreporting has presumably occurred to a similar extent in death certificates of diabetic and nondiabetic patients. As to NVNA-related CLD, we have previously mentioned that this category is made essentially by NAFLD but that it also includes other etiologies (e.g., toxic substances, autoimmunity, hemocromatosis). Even though these etiologies might be slightly more frequent in diabetes, they are, however, rather uncommon. Therefore, we feel that our data are solid enough to suggest an increased risk of mortality by NAFLD in diabetes.

Table 4. SMRs for CLDs reported as either the underlying or the contributing causes of death of 167,621 diabetic patients followed-up for 3 years

	Men		Women	
	n	SMR (CI)	*n*	SMR (CI)
All ages				
All CLD	825	2.54 (2.37–2.72)	358	2.58 (2.32–2.87)
Virus-related CLD[a]	124	2.28 (1.90–2.72)	110	2.05 (1.69–2.47)
Alcohol-related CLD[a]	222	2.25 (1.96–2.56)	38	2.26 (1.60–3.11)
NVNA-related CLD	495	2.78 (2.54–3.04)	212	3.07 (2.67–3.51)
30–64 years				
All CLD	230	3.84 (3.36–4.37)	41	4.79 (3.44–6.50)
Virus-related CLD[a]	30	3.21 (2.16–4.58)	6	4.85 (1.77–10.6)
Alcohol-related CLD[a]	77	3.34 (2.63–4.17)	12	3.71 (1.91–6.47)
NVNA-related CLD	132	4.41 (3.69–5.23)	23	5.51 (3.49–8.26)
65–74 years				
All CLD	329	2.51 (2.24–2.79)	100	3.17 (2.58–3.85)
Virus-related CLD[a]	52	2.60 (1.94–3.41)	31	3.27 (2.22–4.65)
Alcohol-related CLD[a]	81	1.93 (1.53–2.39)	17	2.72 (1.58–4.35)
NVNA-related CLD	198	2.82 (2.44–3.24)	54	3.31 (2.49–4.32)
75–89 years				
All CLD	266	1.99 (1.76–2.24)	217	2.21 (1.92–2.52)
Virus-related CLD[a]	42	1.69 (1.22–2.28)	73	1.70 (1.33–2.14)
Alcohol-related CLD[a]	64	1.90 (1.47–2.43)	9	1.23 (0.56–2.34)
NVNA-related CLD	165	2.12 (1.81–2.47)	135	2.78 (2.33–3.28)

CI, confidence interval; CLD, chronic liver disease; NVNA, non-viral non-alcohol; SMR, standardized mortality ratio.
[a]18 CLD deaths were classified as related to both alcohol and viral hepatitis.

In conclusion, our study shows that diabetic patients are exposed to a two- to threefold increased risk of mortality from CLD. This increased risk mainly accounts for the hepatic insults apparently different from those by classic viruses and alcohol. With the limitations we have mentioned, the main cause of the excess mortality related to CLD seems to be attributable to NAFLD. For such reasons, strategies to prevent CLD-related deaths should include not only vaccination against viral hepatitis and education on the particularly deleterious effects of alcohol in diabetes but also effective campaigns to reduce body weight and avoid weight gain. An early diagnosis and treatment of NAFLD, if any, might also have a beneficial clinical impact on the survival of diabetic patients.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ It is known that mortality from chronic liver diseases increases in diabetes.
- ✓ The impact of different liver disease etiologies on mortality in diabetes is poorly documented.

WHAT IS NEW HERE

- ✓ All the principal chronic liver disease etiologies examined in the present study increased the risk of mortality in diabetes.
- ✓ Nonalcoholic fatty liver disease emerged as the most important cause of mortality among the different etiologies.

CONFLICT OF INTEREST

Guarantor of the article: Giacomo Zoppini, MD, PhD.

Specific author contributions: U.F. and N.G. designed the study, collected and analyzed the data; G.Z. revised the results and wrote the manuscript; E.B., G.T., and M.S. critically revised the manuscript. All authors have seen and approved the final version of the submitted manuscript.

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