Diabetes Increases the Risk of Acute Hepatic Failure

HASHEM B. EL–SERAG* and JAMES E. EVERHART†

*Sections of Gastroenterology and Health Services Research, Houston Department of Veterans Affairs Medical Center; Baylor College of Medicine, Houston, Texas; and †National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland

Background & Aims: **It is unclear whether patients with diabetes are at an increased risk of developing acute liver failure (ALF). We performed a large cohort study to examine the occurrence of ALF by using the databases of the Department of Veterans Affairs.** ***Methods:*** **We identified all patients with a hospital discharge diagnosis of diabetes (ICD-9 codes: 250 [1–9][0–4]) from 1985 to 1990 and randomly assigned patients without diabetes for comparison (3:1 ratio). We excluded patients with concomitant liver disease as far back as 1980. After excluding the first year of follow-up, the remaining patients were observed through 2000 for the occurrence of ALF (ICD-9 570). The cumulative risk and the relative risk of ALF were determined by Kaplan–Meier and Cox Proportional Hazard survival analysis, respectively.** ***Results:*** **We included 173,643 patients with diabetes and 650,620 patients without diabetes. Patients with diabetes were significantly older (62 vs. 54 years) and were less likely to be white (28% vs. 24%). The cumulative risk of ALF was significantly higher among patients with diabetes (incidence rate, 2.31 per 10,000 vs. 1.44 per 10,000 person-years; $P < 0.0001$). In the Cox proportional hazard model, diabetes was associated with a relative risk of 1.44 (95% CI, 1.26–1.63; $P < 0.0001$) for ALF while controlling for comorbidity index, age, sex, ethnicity, and period of service. This risk remained significantly increased after excluding patients with liver disease or viral hepatitis recorded during follow-up or those with ALF recorded after the introduction of troglitazone (relative risk = 1.40; $P < 0.0001$).** ***Conclusions:*** **Diabetes increases the risk of ALF. The increase in ALF is independent of recognized underlying chronic liver disease or viral hepatitis.**

Persons with diabetes mellitus are at an increased risk of developing a variety of liver diseases. Diabetes predisposes to nonalcoholic fatty liver disease, including nonalcoholic steatohepatitis. Nonalcoholic steatohepatitis may progress in 5%–20% of cases to cirrhosis.[1] Diabetes and insulin resistance have been reported to be independent risk factors for advanced fibrosis and cirrhosis among patients with nonalcoholic steatohepatitis.[2–4] The risk of developing hepatocellular carcinoma may also be increased in persons with diabetes,[5–7] particularly among patients with other causes of chronic liver disease, such as hepatitis C virus or alcoholic cirrhosis.[8] Recent articles have shown fulminant hepatic failure among diabetics that is related to the use of the hypoglycemic agent troglitazone.[9–12] However, apart from these case reports, it remains unknown whether diabetes increases the risk for fulminant hepatic failure among troglitazone nonusers.

The Department of Veterans Affairs (VA) is one of the largest health care providers in the United States. The computerized database of the VA, the Patient Treatment File (PTF), registers patients' information from 172 VA hospitals throughout the United States. By using information contained in these databases, we have examined the incidence of acute liver failure in a large cohort of hospitalized veterans with diabetes.

Methods

Databases

The study population was assembled from hospitalized veterans registered within the nationwide PTF. The PTF comprises a multitude of annual data files in which discharge diagnoses are recorded for each inpatient hospital visit since 1970. Individual patients can be traced through the annual files of the PTF through their unique social security numbers. Since 1981, discharge diagnoses have been coded according to the 9th revision of the Clinical Modification of International Classification of Diseases (ICD-9-CM).[13] The PTF does not contain information about pharmacy or laboratory test results.

The Beneficiary Identification and Records Locator Subsystem (BIRLS) file contains claims and benefits paid to veterans and their beneficiaries. The Mini-BIRLS Death File of the PTF contains 1 record for each veteran in the BIRLS file that has a date of death recorded. Because of various incentives, up to 90% of deaths among veterans are captured by the BIRLS file.[14–16]

Abbreviations used in this paper: BIRLS, Beneficiary Identification and Records Locator Subsystem; ICD, International Classification of Diseases; PTF, Patient Treatment File; VA, Department of Veterans Affairs.

0016-5085/02/$35.00
doi:10.1053/gast.2002.33650

Study Population

The study population comprised all hospitalized patients with diabetes, as defined by discharge diagnosis codes (ICD-9 250 [1–9][0–4]),[13] during the 5-year period from October 1985 to October 1990. For comparison, we randomly assigned 3 patients without diabetes for every patient with diabetes matched on the year of hospitalization. We included only adults (older than 20 years). A method of random selection without replacement was used to ensure that no individual control subject was selected more than once. The sampling frame for groups of patients with and without diabetes was individual patients, rather than hospitalizations. Patients with multiple hospitalizations were counted only once, and their earliest hospitalization date was chosen to be the index hospitalization.

By using the social security number as a unique identifier, the remaining patients were prospectively observed in the annual PTF and BIRLS death files until the end of fiscal year 2000. These files were searched for the occurrence of diagnoses of acute liver failure (ICD-9 570), as well as death (in BIRLS), in both groups of patients. We also searched the PTF for other causes of acute liver failure and conditions that could be confused with acute liver failure. These included hepatitis C (ICD-9 codes 070.41, 070.44, 070.51, 070.54, and V02.62); hepatitis B (070.20–070.23, 070.30–070.33, and V02.61); heart failure (428.0, 428.1, and 428.9); hepatitis A (070.0 and 070.1); liver abscess (572.0 and 572.1); fatty liver (571.0 and 571.8); chronic liver disease, including alcoholic liver disease and cirrhosis (571.1–571.3, 571.40, 571.41, 571.49, 571.5, 571.6, 571.9, 572.2, 572.3, and 572.8); alcoholism (all codes starting with 303, and 790.3); abnormal liver enzymes (790.4); hemochromatosis (275.0); and hepatocellular carcinoma (155.0).

To increase the probability of capturing new (incident) cases of acute liver failure, we excluded from both groups patients with acute or chronic liver disease recorded during the index hospitalization or during any previous hospitalization dating back to 1980. We also excluded all patients who had any diagnosis of acute or chronic liver disorder during the first year that followed their index hospitalization. During subsequent follow-up (after the first year), the presence of liver disease (chronic liver disease, including alcohol-related liver disease, cirrhosis, viral hepatitis [B or C], fatty liver, liver abscess, and hepatocellular carcinoma) was identified and recorded. The time at risk of acute liver failure was measured from 1 year after the index hospitalization until October 2000 or the development of acute liver failure or death.

The inpatient files were searched for a number of conditions during the initial hospitalization to calculate the Deyo comorbidity index, which is a modification of the Charlson disease severity index.[17] This index is commonly used to adjust for the effect of comorbidities when using administrative data in comparative studies. These conditions included the following: acquired immunodeficiency syndrome (042–044); cerebrovascular disease (430–438); chronic pulmonary disease (490–496, 500–505, and 506.4); congestive heart failure (428.0–428.9); dementia (290.0–290.9); diabetes with complications (250–250.3); hemiplegia or paraplegia (344.1 and 342–342.9); myocardial infarction (410.0–410.9 and 412); peptic ulcer disease (531–534.9); peripheral vascular disease (443.9, 441.0–441.9, 785.4, and V43.4); renal disease (582–582.9, 583–583.7, 585, 586, and 588–588.9); metastatic solid tumors (196–199.1); any malignancy, including lymphoma and leukemia (140–172.9, 174–195.8, and 200–208.9); and rheumatologic disease (710.0, 710.1, 710.4, 714.0–714.2, 714.81, and 725). In constructing the index, we did not include diabetes only (absent by definition from the control group) or liver disease (absent in both groups by definition). The composite score for the Deyo comorbidity index at the initial hospitalization was compared between patients with diabetes and those without. The comorbidity index was also included as a covariate in the multiple regression analyses.

Statistical Analyses

Baseline demographic features were compared between patients with and those without diabetes; χ^2 tests were used for univariate comparisons between dichotomous variables, whereas unpaired *t* tests were used to compare continuous variables. The cumulative risk of acute liver failure was estimated in a Kaplan–Meier survival analysis. The log-rank test was used to test the statistical significance for differences in the rates of acute liver failure between patients with and those without diabetes. The occurrence of acute liver failure was modeled as the outcome variable in a Cox proportional hazard survival analysis that examined the risk associated with diabetes while controlling for age, sex, ethnicity, period of military service, hepatitis C virus, hepatitis B virus, chronic liver disease, and the Deyo comorbidity index. Separate models were used to examine the same associations after excluding patients with any liver disease, alcoholism, abnormal liver tests, or those with risk factors for acute liver failure (viral hepatitis and heart failure) that were recorded during the follow-up period, including those recorded in the index hospitalization. The models were tested for the presence of statistical interactions among the potential risk factors. Wald's χ^2 tests were used to test for the significance of the influence for each risk factor. Hazard rate ratios and their 95% confidence intervals were presented for each estimate to represent the relative risk. The log-log survival plots were used to examine the proportional hazards assumption, which was met in all models. All analyses were performed with SAS (SAS Institute, Cary, NC).[18]

Results

We identified 257,649 patients with diabetes and 772,947 patients without diabetes who were hospitalized in VA facilities between October 1985 and October 1990. Of these, 216,831 patients with diabetes and 765,853 patients without diabetes did not have liver disease in their hospitalization records as far back as 1980. After excluding all patients in whom liver disease

was recorded during the first year of follow-up, 173,643 patients with diabetes and 650,620 patients without diabetes remained and were included in the principal analysis of acute liver failure. The demographic features for these patients are shown in Table 1. Patients with diabetes were an average of 8 years older and were less likely to be white or belong to a Vietnam period of service (not necessarily serving in Vietnam) than patients without diabetes. The majority (99.5%) of diabetic patients had type II diabetes mellitus. The translation of the Charlson comorbidity index into ICD-9-CM codes includes 14 diagnostic categories (see Methods). With a Mantel-Haenszel χ^2 test, there was no significant difference between cases and controls in these comorbid conditions at the initial hospitalization (2.96; $P = 0.09$). For example, myocardial infarction was diagnosed in 8.7% of cases with diabetes and 8.6% of controls without diabetes; congestive heart failure in 4.9% of cases and 4.9% of controls; peripheral vascular disease in 1.7% of cases and 1.6% of controls; and cerebrovascular disease in 0.6% of cases and controls. An average comorbidity score that reflects the presence or absence of all of the 14 diagnostic categories was calculated for each person in the study; this variable was included in the regression analyses described below.

During follow-up of 1,494,995 patient-years with diabetes, 346 patients developed acute liver failure (incidence rate, 2.31 per 10,000 person-years); during follow-up of 6,556,350 patient-years without diabetes, 942 patients developed acute liver failure (incidence rate, 1.44 per 10,000 person-years). During follow-up that ended in October 2000, the Kaplan–Meier survival analysis showed a significantly higher cumulative incidence of acute liver failure among patients with diabetes compared with those without diabetes (0.30% vs. 0.19%; $P < 0.0001$; Figure 1). The 6-week mortality after hospitalization with acute liver failure was 60% for patients with diabetes and 63% for those without diabetes ($P > 0.05$).

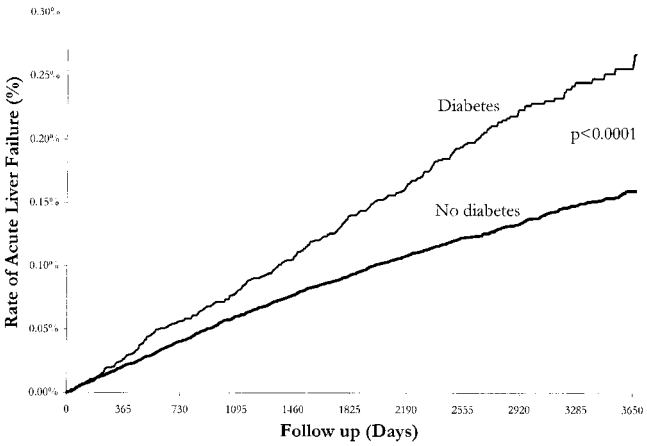

Figure 1. The cumulative risk of acute liver failure among veteran patients hospitalized during 1985–1990. No patient had acute or chronic liver disease recorded before, during, or 1 year after their index hospitalization. The follow-up period ended in October 2001. The upper line represents acute liver failure recorded after the first year of index hospitalization in patients with diabetes, whereas the lower line represents the same outcome in patients without diabetes. Acute liver failure was significantly higher in patients with diabetes ($P < 0.0001$).

In the Cox proportional hazard analysis, diabetes was associated with a relative risk of acute liver failure of 1.44 (95% confidence interval, 1.26% to 1.63%; $P < 0.0001$). This adjusted relative risk was obtained while controlling for differences in age, sex, ethnicity, Deyo comorbidity index, and period of service (Table 2). In a separate model, we also controlled for the presence of chronic liver disease, including alcoholic liver disease and cirrhosis, that was recorded during follow-up. In that model, diabetes remained an independent risk for acute liver failure, with an adjusted relative risk of 1.44. In the

Table 1. A Comparison of Demographic Characteristics and Major Risk Factors Between Cases With Diabetes and Controls Without Diabetes

Variable	Cases (n = 173,643)	Control (n = 650,620)	P value
Age, yr, mean (±SD)	61.7 (±10)	54.5 (±12)	<0.0001
Men	170,944 (98.4%)	635,005 (97.6%)	<0.0001
Ethnicity: Non-Hispanic, White	124,361 (71.6%)	496,290 (76.3%)	<0.0001
Period of military service (Vietnam era)	23,308 (13.4%)	175,949 (27.0%)	<0.0001

Table 2. Risk Factors for Acute Liver Failure: Results of Multivariate Cox Proportional Hazard Analysis in a Cohort of 824,263 Hospitalized Veterans During 1985–1990 With No Prior Liver Disease, While Adjusting for the Comorbidity Index

Variable	Adjusted hazard ratio	95% Confidence interval	P value
Diabetes	1.44	1.26–1.63	<0.0001
Older age (per 10 yr)	1.88	1.40–2.51	<0.0001
Women	1.12	0.79–1.61	0.5261
Hispanic (vs. non-Hispanic, white)	0.83	0.56–1.22	0.3395
Black (vs. non-Hispanic, white)	0.96	0.83–1.11	0.5801
Vietnam era (vs. non-Vietnam)	1.06	0.90–1.23	0.5045
Chronic liver disease (including cirrhosis)[a]	14.31	12.55–16.3	<0.0001

[a]Recorded during follow-up.

Table 3. Risk Factors for Acute Liver Failure: Results of Multivariate Cox Proportional Hazard Analysis in a Cohort of 797,551 Hospitalized Veterans During 1985–1990 With No Prior Chronic Liver Disease (Including Alcoholic), Liver Abscess, Hepatocellular Carcinoma, Hemochromatosis, Viral Hepatitis, or Concomitant Congestive Heart Failure

Variable	Adjusted hazard ratio	95% Confidence interval	*P* value
Diabetes	1.43	1.25–1.67	<0.0001
Older age (per 10 yr)	1.92	1.27–2.88	<0.0001
Women	1.30	0.89–1.92	0.1898
Hispanic (vs. non-Hispanic, white)	0.77	0.49–1.22	0.2674
Black (vs. non-Hispanic, white)	1.03	0.87–1.22	0.7270
Vietnam-era veteran (vs. non-Vietnam)	1.00	0.79–1.19	0.7791
Comorbidity index	1.03	0.97–1.09	0.3203

same analysis, a diagnosis of chronic liver disease proved to be a strong predictor of acute liver failure, with a relative risk of 14.3 (Table 3). Chronic liver disease was also a strong risk factor in a model that did not include diabetes as a covariate (relative risk = 13.5). Increasing age was also associated with acute liver failure. After controlling for the older age of the diabetic group, the effect of Vietnam period of service was no longer significant.

Of patients who developed acute liver failure, 20% had chronic liver disease (including cirrhosis and alcoholic liver disease; ICD-9 571.1–571.3, 571.40, 571.41, 571.49, 571.5, 571.6, 571.9, 572.2, 572.3, and 572.8) recorded after the first year of follow-up, 2% had fatty liver, 1% had hepatocellular carcinoma, 12% had alcoholism, 1% had liver abscess, and 0.2% had abnormal liver enzymes with no documented specific liver disease. However, most patients who developed acute liver failure (70%) had no documented past or concomitant liver disease or alcoholism. Patients with diabetes and acute liver failure had a concurrent diagnosis of congestive heart failure (31%) more often than patients without diabetes who had acute liver failure (22%). When the Cox proportional hazard analysis was restricted to patients with no liver disease (chronic liver disease that included cirrhosis and alcoholic liver disease, liver abscess, hepatocellular carcinoma, hemochromatosis, and abnormal liver enzymes), viral hepatitis, or alcoholism before the hospitalization with acute hepatic failure and no concurrent diagnosis of congestive heart failure, the adjusted relative risk for diabetes remained significantly increased (1.43, 1.25–1.67; $P < 0.0001$). Further exclusion of patients with fatty liver did not change the results appreciably (1.41; 95% confidence interval, 1.22–1.63; $P < 0.0001$). All models were also adjusted for the Deyo comorbidity index.

Troglitazone, a hypoglycemic drug linked to fulminant hepatic failure, was introduced to the VA pharmacy in 1998. When the follow-up of the study cohort was restricted to the end of 1997, the rate of acute liver failure remained higher among patients with diabetes in Kaplan–Meier analysis (0.28% vs. 0.17%; $P < 0.0001$) and in the Cox proportional hazard model (1.40, 1.22–1.61; $P < 0.0001$) (Figure 2).

Discussion

We are unaware of other studies that have specifically examined the incidence of acute liver failure in diabetic patients. In this large cohort study, we found that diabetes mellitus was associated with an approximately 1.5-fold increase in the risk of acute hepatic failure. This increased risk was not fully explained by the presence of underlying liver disease or concomitant known risk factors, such as viral hepatitis, chronic liver disease, alcoholism, congestive heart failure, or other major nonhepatic comorbid illness. The risk of acute liver failure associated with diabetes also predated the introduction of troglitazone.

Diabetes can be a result of severe liver disease. For example, it is reported that 10% to 20% of patients with cirrhosis may have overt diabetes mellitus, and a larger fraction have impaired glucose tolerance.[19,20] Moreover,

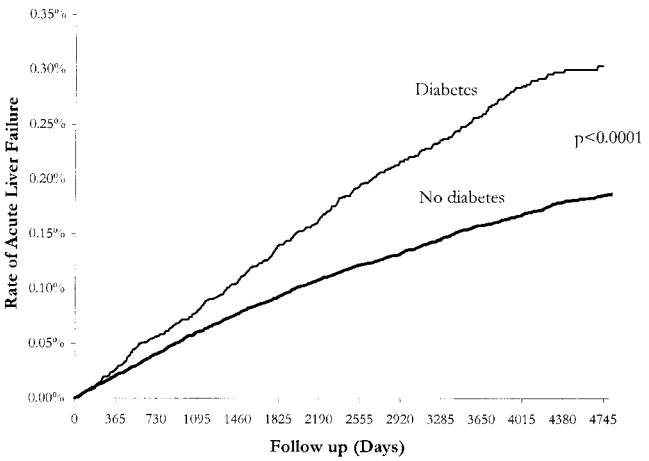

Figure 2. The cumulative risk of acute liver failure among veteran patients hospitalized during 1985–1990. No patient had acute or chronic liver disease recorded before, during, or 1 year after their index hospitalization. The follow-up period was restricted up to *October 1997* (before the introduction of troglitazone to the VA pharmacy in 1998). The upper line represents acute liver failure recorded after the first year of index hospitalization in patients with diabetes, whereas the lower line represents the same outcome in patients without diabetes. Acute liver failure was significantly higher in patients with diabetes ($P < 0.0001$).

uncontrolled diabetes was also reported to accompany fulminant liver failure.[21] Therefore, to avoid inclusion of patients with diabetes secondary to liver disease, we excluded all cases of liver disease before the identification of all patients, as well as those recorded during the first year of follow-up. The use of the VA PTF facilitated the identification of a large cohort of patients with diabetes and the random identification of controls without diabetes from the same hospitalization files. By including many thousands of patients, the study design allowed the detection of a modest increased risk of acute liver failure that might be missed in a smaller study.

Misdiagnosis of both the risk factor of interest (diabetes) and outcome (acute liver failure) are potential concerns in large administrative data sets, in which diagnoses cannot be verified. Although the vast majority of patients with a diagnosis of diabetes actually have diabetes, the disease is frequently not recognized and is underreported on medical records. Thus, there were certainly patients in the nondiabetic group who actually had diabetes. This misclassification would tend to diminish the true effect of diabetes. Although the validity of the ICD-9 code as an indicator of acute liver failure is not known, the high mortality after hospitalization with acute liver failure (more than 60% during the first 6 weeks) is consistent with carefully documented results[22] and argues against an erroneous inclusion of a significant number of cases with mild or chronic liver disease. In addition, the same code was used to define acute liver failure in patients with and without diabetes, and the mortality rates for these groups were not different. Although it is unlikely that acute liver failure is overlooked as a diagnosis, it is possible that patients receive this diagnosis in whom the liver injury is secondary to another disorder. Such misclassification with acute liver failure would most likely occur with congestive heart failure and "shock liver," which is more common among diabetics. Therefore, we also performed an analysis that excluded patients with concurrent diagnoses of acute liver failure and congestive heart failure. The relative risk was slightly reduced but remained highly statistically significant. Other potential confounders include chronic liver disease, liver abscess, fatty liver, and hepatocellular carcinoma, all of which are known to be more common among diabetics and also increase the risk of acute hepatic failure. Patients with diabetes have also been reported to have higher rates of infectious hepatitis, especially hepatitis C virus and hepatitis B virus, possibly related to needle use.[23,24] In this study, however, diabetes remained an independent risk factor of acute hepatic failure even after we excluded patients with concurrent chronic liver disease, liver abscess, fatty liver, hepatocellular carcinoma, and infectious hepatitis.

This study shows that people with diabetes are at increased risk of acute hepatic failure, but the reasons for the increased risk are uncertain. From other reports of acute hepatic failure, we speculate that most of the patients would have had drug-related liver injury. The largest series of acute liver failure in the United States showed that drugs were the most common cause of liver failure.[22] Although viral hepatitis is also a common cause of acute liver failure, our results changed little with exclusion of these conditions with acute liver failure diagnosis. Furthermore, some causes of liver failure, such as Wilson disease and autoimmune hepatitis, would not be expected in this generally older population of men. If drug-related hepatotoxicity is the main reason for the increased risk among persons with diabetes, then diabetics are either more susceptible to liver injury from drugs or they have greater exposure to hepatotoxic medications. It is quite possible that both increased susceptibility and exposure contributed to the increased risk. The fatty liver and steatohepatitis associated with diabetes are known to cause mitochondrial injury[25] and other hepatocellular dysfunction,[1] which would increase susceptibility to injury. Although excluding persons with recorded fatty liver did not change our results, this diagnosis may be underreported. In the setting of insulin deficiency or insulin resistance, there is increased lipolysis with release of free fatty acids, which are taken up by the liver. Free fatty acids are potentially cytotoxic and cause mitochondrial swelling, increased lysosomal fragility, and impairment of cellular membranes.[26] Patients with diabetes have higher levels of plasma free fatty acids as compared with nondiabetics.[27] Diabetics may also have a greater exposure to dose-dependent or idiosyncratic hepatotoxins, because they typically take several medications, both for diabetes and for associated conditions such as hypertension, heart disease, and hyperlipidemia. In the general population, more than half of people with diabetes took 3 or more prescription medications.[28] Because the VA database did not contain pharmacy information, we could not establish which, if any, medications were causing the increased risk. We do know that one hypoglycemic agent, troglitazone, was implicated in several cases of acute liver failure in the late 1990s.[9–12] However, in this study, limiting our follow-up to the time before the availability of troglitazone had no effect on the relative risk of diabetes for acute liver failure.

Differences in comorbid illness between diabetics and nondiabetics could affect the occurrence of acute liver failure, either directly or indirectly, through the use of

multiple potentially hepatotoxic drugs. For every patient in the study, we calculated the Deyo comorbidity index, which is a modification of Charlson comorbidity index.[17] The presence of major nonhepatic diseases was assessed in this study in both diabetics and nondiabetics. There were no statistically significant differences between the 2 groups in the composite score of the comorbidity index. Moreover, including the comorbidity index as a covariate in the regression model had little effect on the results, with diabetes remaining as an independent risk factor for acute liver failure.

To our knowledge, this study provides the first estimate of the incidence of acute liver failure in a defined population in the United States. Although hospitalized, predominantly male veterans are not representative of the United States population, the incidence rate of 1.44 per 10,000 person-years for nondiabetic veterans provides a benchmark for other studies of acute liver failure. Although the absolute rate of acute liver failure was low, over the course of the study, 130 excess cases of acute liver failure occurred among diabetics. Considering a 60% death rate with acute liver failure, there was an excess of 78 deaths because of this condition among diabetics during the period of the study.

In addition to diabetes, increasing age and the presence of chronic liver disease increased the rate of acute liver failure. As with diabetes, older persons may have both greater susceptibility to acute hepatic failure and more exposures. The increased risk associated with a history of chronic liver disease shows the potential concern with making an accurate diagnosis of acute hepatic failure. Whereas acute hepatic failure may be more likely in patients with chronic liver disease, it is also possible that the final stages of chronic end-stage liver disease can be confused with acute hepatic failure when there is not sufficient information about the preexisting chronic disease. This is a diagnostic challenge that should be addressed in future large-scale studies of acute hepatic failure.

In summary, we found diabetes mellitus to be associated with an increase in the risk of acute liver failure. Older age and the presence of chronic liver disease further increase the risk of this highly fatal condition. Periodic monitoring of liver enzymes and caution in the use of potentially hepatotoxic drugs may be warranted in patients with diabetes. Studies are needed to examine the possible mechanisms of acute liver failure in diabetes.

References

1. Reid AE. Nonalcoholic steatohepatitis. Gastroenterology 2001; 121:710–723.
2. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121:91–100.
3. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116:1413–1419.
4. Marchesini G, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ, Forlani G, Melchionda N. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med 1999;107:450–455.
5. La Vecchia C, Negri E, Decarli A, Franceschi S. Diabetes mellitus and the risk of primary liver cancer. Int J Cancer 1997;73:204–207.
6. Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekbom A, Wolk A, McLaughlin JK, Fraumeni JF Jr. Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst 1996;88:1472–1477.
7. Lagiou P, Kuper H, Stuver SO, Tzonou A, Trichopoulos D, Adami HO. Role of diabetes mellitus in the etiology of hepatocellular carcinoma. J Natl Cancer Inst 2000;92:1096–1099.
8. El-Serag HB, Richardson P, Everhart JE. The role of diabetes in hepatocellular carcinoma among veterans: a case-control study. Am J Gastroenterol 2001;96:2462–2467.
9. Murphy EJ, Davern TJ, Shakil AO, Shick L, Masharani U, Chow H, Freise C, Lee WM, Bass NM. Troglitazone-induced fulminant hepatic failure. Acute Liver Failure Study Group. Dig Dis Sci 2000; 45:549–553.
10. Booth AM, Caldwell SH, Iezzoni JC. Troglitazone-associated hepatic failure. Am J Gastroenterol 2000;95:557–558.
11. Menon KVN, Angulo P, Lindor KD. Severe cholestatic hepatitis from troglitazone in a patient with nonalcoholic steatohepatitis and diabetes mellitus. Am J Gastroenterol 2001;96:1631–1634.
12. Li H, Heller DS, Leevy CB, Zierer KG, Klein KM. Troglitazone-induced fulminant hepatitis: a report of a case with autopsy findings. J Diabetes Complications 2000;14:175–177.
13. Department of Health and Human Services. The international classification of diseases. 9th rev., clinical modification, 3rd ed. Vol. 1: Diseases: tabular list. DHHS publication no. PHS 89-1260. Government Printing Office, Washington, DC, 1989.
14. Boyko EJ, Koepsell TD, Gaziano JM, Horner RD, Feussner JR. US Department of Veterans Affairs medical care system as a resource to epidemiologists. Am J Epidemiol 2000;151:307–314.
15. Page WF. VA mortality reporting for World War II army veterans. Am J Epidemiol 1992;82:124–125.
16. Page WF, Mahan CM, Kang HK. Vital status ascertainment through the files of the department of Veterans Affairs and the social security administration. Ann Epidemiol 1996;6:102–109.
17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use of the ICD-9-CM in administrative databases. J Clin Epidemiol 1992;45:613–619.
18. SAS Institute Inc. SAS/STAT user's guide: basics. Version 6. SAS Institute Inc., Cary, NC, 1990.
19. Kingston ME, Ali MA, Atiyeh M, Donnelly RJ. Diabetes mellitus in chronic active hepatitis. Gastroenterology 1984;87:688–694.
20. Gentile S, Loguercio C, Marmo R, Carbone L, Del Vecchio Blanco C. Incidence of altered glucose tolerance in cirrhosis. Diabetes Res Clin Pract 1993;22:37–44.
21. Matz R. Diabetes with liver failure. Lancet 1972;1:851–852.
22. Schiodt FV, Atillasoy E, Shakil AO, Schiff ER, Caldwell C, Kowdley KV, Stribling R, Crippin JS, Flamm S, Somberg KA, Rosen H, McCashland TM, Hay JE, Lee WM. Etiology and outcome for 295 patients with acute liver failure in the United States. Liver Transpl Surg 1999;5:29–34.
23. Silverman JF, Pories WJ, Caro JF. Liver pathology in diabetes mellitus and morbid obesity. Pathol Annu 1989;24:275–302.
24. Khuri KJ, Shammaa MH, Abourizk N. Hepatitis B virus markers in diabetes mellitus. Diabetes Care 1985;8:250–253.

25. Pessayre D, Berson A, Fromenty B, Mansouri A. Mitochondria in steatohepatitis. Semin Liver Dis 2001;21:57–69.
26. Acosta D, Wenzel DG. Injury produced by free fatty acids to lysosomes and mitochondria in cultured heart muscles and endothelial cells. Atherosclerosis 1974;20:417–426.
27. Bogardus C, Lillioja S, Howard BV, Reaven G, Mott D. Relationships between insulin secretion, insulin action, and fasting plasma glucose concentration in nondiabetic and noninsulin-dependent diabetic subjects. J Clin Invest 1984;74:1238–1246.
28. Harris MI. Health care and health status and outcomes for patients with type 2 diabetes. Diabetes Care 2000;23:754–758.

Received November 20, 2001. Accepted February 28, 2002.

Address requests for reprints to: Hashem B. El-Serag, M.D., M.P.H., The Houston Veterans Affairs Medical Center (152), 2002 Holcombe Blvd., Houston, Texas 77030. e-mail: hasheme@bcm.tmc.edu; fax: (713) 748-7359.

Dr. El-Serag is a Veterans Affairs Health Services Research and Development Awardee (RCD00-013-2).