CHAPTER 26

LIVER AND GALLBLADDER DISEASE IN DIABETES

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SUMMARY

This chapter focuses on the relationships of three common chronic liver diseases—nonalcoholic fatty liver disease (NAFLD), viral hepatitis, and cirrhosis—and of gallstone disease with diabetes.

NAFLD requires finding fat (steatosis) in the liver in the absence of heavy alcohol consumption and other secondary causes of hepatic steatosis. In a nationally representative sample of the U.S. population, the prevalence of NAFLD assessed by ultrasonography was greater among persons with diagnosed (45.5%) and undiagnosed (43.1%) diabetes and prediabetes (24.9%) compared to those with normal glucose (15.9%). Diabetes and insulin resistance are thought to be closely linked to the development and progression of NAFLD. However, there is also evidence that NAFLD increases the risk of diabetes. The risk of incident diabetes was at least twice as high among persons with NAFLD in several prospective studies that defined NAFLD based on elevated liver enzymes.

Hepatitis C virus (HCV) infection has been associated with an increased risk of diabetes, although results of population-based studies have been inconsistent. In contrast, there is little evidence that hepatitis B virus (HBV) infection increases the risk of diabetes. In a nationally representative sample of the U.S. population, HCV infection (HCV antibody positive) was not associated with diabetes (odds ratio [OR] 0.8) or prediabetes (OR 1.0). Similarly, HBV infection (HBV core antibody positive) was unrelated to diabetes (OR 1.0) and prediabetes (OR 1.1).

Diabetes is found in a high proportion of patients with cirrhosis (35%–71%), regardless of the liver disease etiology. Furthermore, the proportion of diabetes among those with cirrhosis is particularly high (as much as 71%) in studies that have included oral glucose tolerance testing. Among patients listed as candidates for liver transplantation, more than one-quarter carry a diagnosis of diabetes, which is double the proportion 20 years ago. Patients with diabetes awaiting liver transplantation have an increased risk of removal from the waiting list due to dying before transplantation or to deteriorating health resulting in medical contraindications to transplantation (OR 1.2). After liver transplantation, new-onset diabetes has been commonly reported (as high as 54% of HCV positive patients), usually among patients without adequate glucose testing before transplantation.

Finally, a high prevalence of gallstone disease (gallstones or history of cholecystectomy) was documented by ultrasound among persons with diagnosed (33.3%) and undiagnosed (23.3%) diabetes and prediabetes (20.8%) compared to persons with normal glucose (16.7%) in a nationally representative sample of the U.S. population. This relationship was present across demographic subgroups, for both gallstones and cholecystectomy. Review of published epidemiologic studies of ultrasound-detected gallstone disease likewise indicates a fairly consistent association of gallstone disease with diabetes independent of adiposity or other shared risk factors. An association of insulin resistance with gallstone disease has also been shown among those without diabetes. For example, gallstone disease was 60% more common among the highest compared to the lowest fasting serum insulin quintile among U.S. women. Insulin resistance may be a link between diabetes and gallstone disease.

INTRODUCTION

This chapter concerns the relationship between diabetes and certain chronic liver diseases and gallstone disease. It does not address all liver diseases, of which there are many, or chronic liver disease in general. Rather, the authors have examined the association of diabetes with a few significant and relatively common liver diseases for which there are national data. These are fatty liver, especially fatty liver in the absence of significant alcohol consumption (nonalcoholic fatty liver disease [NAFLD]), chronic hepatitis C virus (HCV) infection, chronic hepatitis B virus (HBV) infection, and cirrhosis. Hepatocellular carcinoma (HCC) is addressed in Chapter 29 *Cancer and Diabetes*. The significance of diabetes in liver transplantation and its occurrence

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posttransplantation are examined in this chapter. Finally, the association of diabetes with gallstones and cholecystectomy is described.

As the various forms of hepatobiliary disease are discussed in the following sections, the reader is cautioned not to infer causal relationships with diabetes. Diabetes, certain liver diseases, and gallstones share numerous risk factors and pathophysiologic pathways. It has been difficult to establish that one condition precedes another, much less a causal relationship. For example, although a greater than twofold increase in liver disease mortality has been reported among persons with diabetes (1,2), it should not be inferred necessarily that diabetes caused the increase.

DATA SOURCES AND LIMITATIONS

NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS

The National Health and Nutrition Examination Surveys (NHANES) are nationally representative surveys conducted in the United States by the National Center for Health Statistics of the Centers for Disease Control and Prevention to assess the health and nutritional status in the general U.S. population (3). The NHANES consist of interviews, physical examinations, and laboratory tests. The NHANES III (1988–1994) and NHANES 1999–2010 were used in this chapter to generate new data for the U.S. population on the relationships of NAFLD, HCV, HBV, and gallstone disease with diabetes and prediabetes. The NHANES III provided the only national data on hepatic steatosis and on subclinical gallstone disease. Abdominal ultrasonography was performed on adults age 20–74 years who underwent an examination at a mobile examination center in order to identify subclinical gallstone disease. The NHANES III ultrasounds were reviewed in 2009–2010 to identify hepatic steatosis. NHANES serum specimens have been analyzed for markers of HBV (core total antibody [HBcAb] and surface antigen [HBsAg]) and of HCV (antibody and, since 1999, ribonucleic acid [RNA]). The NHANES also provided national data on undiagnosed and diagnosed diabetes. Participants were asked about a health care provider diagnosis of diabetes and had measurements of serum glycosylated hemoglobin (A1c) and fasting plasma glucose. Diabetes is defined in the NHANES III as diagnosed diabetes (self-reported doctor or health professional diagnosis) and, among persons without a diagnosis, as undiagnosed diabetes (A1c ≥6.5% [≥48 mmol/mol] or fasting glucose ≥126 mg/dL [≥6.99 mmol/L]), prediabetes (A1c 5.7%–6.4% [39–46 mmol/mol] or fasting glucose 100–125 mg/dL [5.55–6.94 mmol/L]), or normal glucose levels (A1c <5.7% and fasting glucose <100 mg/dL).

A strength of the NHANES is the large sample that is representative of the general U.S. population. A limitation of these surveys is the cross-sectional design that does not permit determination of temporal relationships between abnormal glucose metabolism and diseases of the liver and gallbladder. An additional limitation of the NHANES III is the use of ultrasound for detection of hepatic steatosis, whereas the criterion standard is a histological diagnosis. Ultrasound was found to be accurate for predicting moderate-severe fatty liver in relation to histology with an area under the receiver operating characteristic curve (AUROC) of 0.93 and a sensitivity of 85% and specificity of 94% in a 2011 meta-analysis (4). However, it is insensitive to mild steatosis and cannot be used to differentiate steatohepatitis from steatosis or to identify fibrosis, so ultrasound may underestimate the true prevalence of fatty liver disease.

SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS

The Scientific Registry of Transplant Recipients (SRTR) is a national database of transplantation statistics that was founded to support the evaluation of the scientific and clinical status of solid organ transplantation, including liver (5). Data are collected by the Organ Procurement and Transplantation Network from hospitals and organ procurement organizations throughout the United States. The SRTR is administered by the Chronic Disease Research Group of the Minneapolis Medical Research Foundation. The SRTR Standard Analysis File (SAF) includes data on all persons in the U.S. population listed as candidates for liver transplantation. Information on diabetes has been included in the SAF since 1994. The SRTR was used in this chapter to examine the relationship of liver transplantation and diabetes in the U.S. population. A limitation of this database is that the quality of the data is unverified. Information on a diabetes diagnosis is self-reported.

NONALCOHOLIC FATTY LIVER DISEASE AND NONALCOHOLIC STEATOHEPATITIS

NONALCOHOLIC FATTY LIVER DISEASE: DESCRIPTION AND DIAGNOSIS

NAFLD is a chronic liver disease that affects people with and without diabetes. NAFLD encompasses a spectrum of liver (histopathologic) abnormalities ranging from a simple accumulation of fat (simple steatosis), to a necroinflammatory condition known as nonalcoholic steatohepatitis (NASH), to various stages of fibrosis, which if advanced, may culminate in cirrhosis. As with other chronic liver diseases, once cirrhosis is present, HCC can occur. In addition, there is growing evidence that HCC can occur in NAFLD even without substantial fibrosis or cirrhosis (6).

Hepatic steatosis has a number of underlying etiologies, including certain medications (e.g., tamoxifen), genetic

metabolic disorders (e.g., Weber-Christian disease), hepatotoxins (e.g., solvents), and nutritional supplementation (e.g., parenteral nutrition). Alcohol consumption is also a major cause of hepatic steatosis. NAFLD is diagnosed when steatosis and/or steatohepatitis are present in the absence of these other underlying causes, including significant alcohol consumption. Although the level of evidence is moderate-low, the 2012 NAFLD guidelines from the American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the American Gastroenterological Association recommend using cutoffs of >21 drinks on average per week in men and >14 drinks on average per week in women as representing significant alcohol consumption (7). Given the propensity of individuals to under-report alcohol consumption, in the analyses conducted for this chapter, excessive alcohol use was defined as >2 drinks per day for men and >1 drink per day for women (8).

NAFLD is a diagnosis confirmed by a liver biopsy, accompanied by a suggestive history and exclusion of other causes of liver disease (7). However, liver biopsies are typically not feasible in population-based epidemiologic studies. Therefore, the diagnosis is usually made using surrogate markers, such as radiologic imaging with ultrasonography, computerized tomography, magnetic resonance (MR) imaging, or less optimally, liver enzymes. Fibroscan®, which can detect liver stiffness as an estimate of fibrosis, was approved in 2013 by the U.S. Food and Drug Administration; however, data acquisition and accuracy appear lower in obese patients compared to those of normal weight. MR elastography, which can accurately estimate fibrosis in a variety of liver diseases, can be affected by inflammation and is expensive and not yet widely available. To date, ultrasound remains the most widely used imaging modality across the United States and worldwide. As with biopsy, these tests are generally used in combination with history and laboratory tests, such that NAFLD is often defined as radiologic evidence of liver fat or abnormal liver enzyme elevation in the absence of significant alcohol consumption, use of some medications, viral hepatitis, or iron overload. These surrogate tests vary widely in their costs, and to date, none has been able to accurately detect inflammation or NASH or to stage fibrosis (9).

The Fatty Liver Index was developed in Italy to more accurately detect fatty liver disease using physical measures and laboratory tests (10). The formula for the Fatty Liver Index is: FLI = ($e^{0.953*\log e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e(\text{ggt}) + 0.053*\text{waist circumference} - 15.745}$) / ($1 + e^{0.953*\log e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e(\text{ggt}) + 0.053*\text{waist circumference} - 15.745}$) * 100 (where GGT is gamma glutamyltransferase and BMI is body mass index). In the initial study, a Fatty Liver Index score <30 had a negative likelihood ratio of 0.2, effectively ruling out fatty liver (sensitivity of 87%), and a score ≥60 had a positive likelihood ratio of 4.3, ruling in fatty liver disease with a specificity of 86%. The Fatty Liver Index has been validated against ultrasound in several studies, with an AUROC of 0.81–0.82 (11,12). It correlates very well with another noninvasive marker, the SteatoTest, that is available clinically and, when using the recommended cutoffs, has a sensitivity of 80.3% and a specificity of 87% compared to ultrasound. Furthermore, the Index was predictive of liver-related mortality in one cohort (13).

It is worth noting that none of these indirect, nonbiopsy measures of NAFLD are reliably able to stage the severity of the disease, correctly identify individuals with NASH, or stage fibrosis. Furthermore, at this time, there is no standard accepted definition of NAFLD in epidemiologic studies, and therefore, estimates of NAFLD prevalence vary widely, even using the same data (such as the NHANES III).

PREVALENCE OF NAFLD IN THE UNITED STATES

Despite the limitations of epidemiologic studies to diagnose NAFLD, it is believed that NAFLD is the most common chronic liver disease in the United States. The estimated prevalence of NAFLD in the United States ranges from 5% to 31% of the general population, depending on the diagnostic method used (14), and is increasing over time (15). NAFLD is strongly associated with obesity, insulin resistance, and type 2 diabetes, which are thought to contribute to the underlying pathophysiology of the disease.

Several studies have used data from the NHANES III to estimate the prevalence of NAFLD in those with and without diabetes (16). In new analyses for *Diabetes in America, 3rd edition*, using abdominal ultrasound data from the NHANES III to detect moderate to severe steatosis, and after excluding heavy drinkers (>2 drinks/day for men or >1 drink/day for women) and standardizing for age, NAFLD was present in 23.9% of adults overall in the general population and affected 45.5% of those with diagnosed diabetes, 43.1% with undiagnosed diabetes, 24.9% with prediabetes, and 15.9% with normal glucose levels (Figure 26.1) (17). The prevalence of NAFLD was higher in middle-aged and older adults, peaking in adults age 45–64 years with diabetes (Table 26.1). NAFLD was more common in men than women and in Mexican Americans compared to whites, with blacks having the lowest prevalence. Among adults with diabetes, however, men and women had the same prevalence, and Mexican Americans and whites had a similar prevalence (Table 26.1).

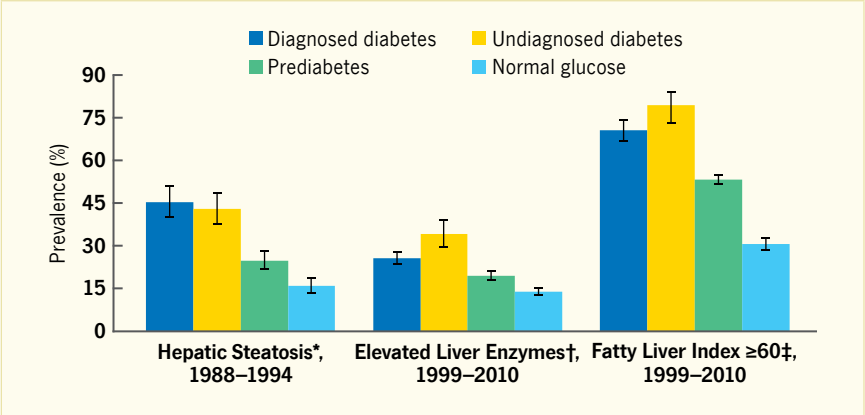
In the NHANES 1999–2010, using the Fatty Liver Index in the fasting sample to detect NAFLD after excluding HBV, HCV, and heavy drinkers, the prevalence of NAFLD was 46.5% in the general population and affected 70.8% of those with diagnosed diabetes, 79.4% with undiagnosed diabetes, 53.3% with prediabetes, and 30.7% with normal glucose levels (Figure 26.1, Table 26.2). Similar to the data from the NHANES III using ultrasound, NAFLD prevalence peaked in middle age, and the difference in prevalence between men and women and across racial/ethnic groups was substantially reduced in people with diabetes (Table 26.2).

Finally, in the NHANES 1999–2010, the prevalence of an elevated aspartate aminotransferase (AST), alanine

aminotransferase (ALT), or GGT was used as a measure of liver injury. (Liver enzyme cutoffs were defined as the 95th percentile in a subgroup of adults at low risk for liver injury, that is: negative for HBsAg and HCV antibody; consumption of ≤2 drinks per day for men or ≤1 drink per day for women; BMI <25 kg/m²; waist circumference ≤102 cm for men or ≤88 cm for women; no health care provider-diagnosed diabetes; and A1c <6.5%.) In the total population, the prevalence of an elevated AST, ALT, or GGT was 19.8% overall, including 26.3% in people with diabetes and 19.1% in those without. Exclusion of heavy drinkers did not substantively change these estimates; 19.1% of adults overall had evidence of probable NAFLD, including 25.7% of those with diabetes and 18.4% of those without diabetes (Figure 26.1, Table 26.3). Using this definition, NAFLD was more common in women and more common among those age 20–44 years with diabetes (32.2%).

In a new analysis for *Diabetes in America*, among persons with diagnosed diabetes, those taking diabetes medications had the same or somewhat increased prevalence of NAFLD defined using the Fatty Liver Index or elevated liver enzymes compared to those not taking the medications (Table 26.4). The two exceptions were those taking thiazolidinediones or insulin. Those taking thiazolidinediones had a lower prevalence of NAFLD than those not taking thiazolidinediones, as defined by elevated liver enzymes (20.6% vs. 27.1%) (Table 26.4), but not by the Fatty Liver Index. This finding is consistent with the results of several treatment trials of NAFLD, which have shown that thiazolidinediones improve steatosis and NASH (18,19) and may improve fibrosis (20). Those taking insulin had a lower prevalence of steatosis on ultrasound (35.8% vs. 49.1%) (Table 26.4), but not by the Fatty Liver Index or liver enzymes. The explanation for this observation is less clear but may reflect patients with more advanced diabetes and more advanced liver disease where steatosis has been replaced by fibrosis. Further research is needed to confirm this finding.

FIGURE 26.1. Age-Standardized Prevalence of Nonalcoholic Fatty Liver Disease, by Diabetes Status, U.S., 1988–1994 and 1999–2010



Diagnosed diabetes is defined as self-reported health care provider diagnosis. Undiagnosed diabetes is defined as glycosylated hemoglobin (A1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL; prediabetes is defined as A1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dL; normal glucose is defined as A1c <5.7% and fasting plasma glucose <100 mg/dL. Data from 1988–1994 are standardized to the National Health Interview Survey 1991 diabetic population age 20–74 years using age categories 20–44, 45–64, and 65–74 years. Data from 1999–2010 are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years. Error bars represent 95% confidence intervals. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.*

* Moderate-severe hepatic steatosis on abdominal ultrasound in NHANES 1988–1994, excluding heavy drinkers (>2 drinks/day for men or >1 drink/day for women).

† Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma glutamyltransferase (GGT) greater than the 95th percentile in adults at low risk for liver injury in NHANES 1999–2010, excluding heavy drinkers and those with viral hepatitis (positive serum markers of hepatitis B or C).

‡ Fatty Liver Index ≥60 in NHANES 1999–2010, excluding heavy drinkers and those with viral hepatitis. The Fatty Liver Index = $(e^{0.953*\log e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e(\text{ggt}) + 0.053*\text{waist circumference} - 15.745})$ / $(1 + e^{0.953*\log e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e(\text{ggt}) + 0.053*\text{waist circumference} - 15.745})$ * 100, where GGT is gamma glutamyltransferase and BMI is body mass index.

SOURCE: National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999–2010

TABLE 26.1. Age-Standardized Prevalence of Nonalcoholic Fatty Liver Disease Diagnosed by Abdominal Ultrasound, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1988–1994

CHARACTERISTICS	PERCENT (STANDARD ERROR)		
	Total	Diabetes	No Diabetes
Total population	23.9 (0.93)	45.5 (2.92)	22.1 (0.90)
Age (years)			
20–44	15.0 (0.85)	35.7 (7.55)	14.7 (0.87)
45–64	26.8 (1.22)	50.1 (3.99)	24.8 (1.23)
65–74	26.4 (1.56)	46.3 (4.63)	23.8 (1.48)
Sex			
Men	26.4 (1.37)	45.4 (5.25)	24.7 (1.24)
Women	21.7 (0.91)	45.4 (3.05)	19.8 (0.84)
Race/ethnicity			
Non-Hispanic white	23.7 (1.09)	47.5 (3.95)	21.9 (1.06)
Non-Hispanic black	20.0 (1.29)	35.3 (3.92)	17.9 (1.16)
Mexican American	36.3 (2.13)	49.5 (3.99)	35.2 (2.23)

Diabetes is defined as self-reported health care provider diagnosis. Nonalcoholic fatty liver disease is defined as moderate-severe hepatic steatosis on abdominal ultrasound, excluding heavy drinkers (>2 drinks/day for men or >1 drink/day for women). Data are standardized to the National Health Interview Survey 1991 diabetic population age 20–74 years using age categories 20–44, 45–64, and 65–74 years.

SOURCE: National Health and Nutrition Examination Survey III 1988–1994

Given the difficulty of diagnosing NAFLD noninvasively with great accuracy, the precision of all of the above estimates is uncertain. What is apparent, however, is that NAFLD is much more common in patients with prediabetes and diabetes and is therefore likely to be important for these populations.

PATHOPHYSIOLOGY AND PROGRESSION OF NAFLD IN RELATION TO DIABETES

The pathogenesis of NAFLD remains unclear, but it may result from any number of insults to the liver (21,22,23,24). A common underlying risk factor is insulin resistance with resulting accumulation of steatosis. Progression to steatohepatitis is thought to be due to additional processes, including inflammation, oxidative stress, and apoptosis leading to fibrosis. Thus, insulin resistance, prediabetes, and diabetes are thought to be closely linked to the development and progression of NAFLD.

Although numerous cross-sectional studies have shown a strong association of diabetes and NAFLD, even after adjustments for body weight and age, prospective studies in humans providing clues to the causal relationships are less clear. Several studies have shown that NAFLD, generally based on indirect markers such as liver enzymes, predicts incident diabetes (25,26,27,28,29,30). In the Insulin Resistance Atherosclerosis Study (IRAS), the highest quartile of ALT compared to the lowest was associated with an adjusted odds ratio (OR) of 2.0 (95% confidence interval [CI] 1.2–3.2) for diabetes as assessed by frequently sampled intravenous glucose tolerance test (28). The findings for AST were similar (adjusted OR 2.0. 95% CI 1.2–3.3). A study in Pima Indians also found an increased risk of diabetes for those with ALT levels at the 90th percentile compared to those at the 10th percentile (adjusted hazard ratio [HR] 1.9, 95% CI 1.1–3.3) (25). An analysis from the Nurses' Health Study showed that both ALT (OR 2.42, 95% CI 1.45–4.04) and GGT (OR 4.84, 95% CI 2.56–9.17) were associated with an increased risk of diabetes when comparing the 5th to the 1st quintile of liver enzyme activity (31).

There is other evidence that insulin resistance and diabetes increase the subsequent risk of NAFLD (32,33). In one 2-year follow-up of a prospective cohort study of workers in Japan, 14% of men and 5% of women developed NAFLD, with a diagnosis based on ultrasonography (33). Both men and women with the metabolic syndrome had a higher odds of developing NAFLD during follow-up compared to those without the metabolic syndrome (adjusted OR 4.0, 95% CI 2.63–6.08 for men and OR 11.20, 95% CI 4.85–25.87 for women). (In that study, the metabolic syndrome was defined by modified third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria as three or more of the following five abnormalities: elevated serum triglyceride level, decreased high-density lipoprotein [HDL] cholesterol level, elevated blood

TABLE 26.2. Age-Standardized Prevalence of Nonalcoholic Fatty Liver Disease Diagnosed by the Fatty Liver Index, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)		
	Total	Diabetes	No Diabetes
Total population	46.5 (0.72)	70.8 (2.02)	43.7 (0.73)
Age (years)			
20–44	34.5 (0.88)	72.9 (5.09)	33.5 (0.87)
45–64	51.3 (1.00)	76.7 (2.92)	48.5 (1.02)
≥65	45.2 (1.18)	63.0 (2.84)	41.7 (1.24)
Sex			
Men	54.1 (1.16)	71.5 (2.89)	51.9 (1.13)
Women	39.9 (0.83)	70.3 (2.60)	36.4 (0.81)
Race/ethnicity			
Non-Hispanic white	46.3 (0.83)	74.5 (2.50)	43.6 (0.84)
Non-Hispanic black	50.7 (1.44)	70.5 (3.43)	46.6 (1.63)
All Hispanic	50.9 (1.69)	66.6 (3.71)	47.9 (1.80)
Mexican American	56.1 (1.62)	74.7 (2.97)	51.6 (1.98)

Diabetes is defined as self-reported health care provider diagnosis. Nonalcoholic fatty liver disease is defined as Fatty Liver Index ≥60, excluding heavy drinkers (>2 drinks/day for men or >1 drink/day for women) and those with viral hepatitis (positive serum markers of hepatitis B or C). The Fatty Liver Index = $(e^{0.953*\log_e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log_e(\text{ggt}) + 0.053*\text{waist circumference} - 15.745}) / (1 + e^{0.953*\log_e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log_e(\text{ggt}) + 0.053*\text{waist circumference} - 15.745}) * 100$, where GGT is gamma glutamyltransferase and BMI is body mass index. Data are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years.

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

TABLE 26.3. Age-Standardized Prevalence of Nonalcoholic Fatty Liver Disease Diagnosed by Elevated Liver Enzymes, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2010

CHARACTERISTICS	PERCENT (STANDARD ERROR)		
	Total	Diabetes	No Diabetes
Total population	19.1 (0.37)	25.7 (1.17)	18.4 (0.40)
Age (years)			
20–44	17.1 (0.48)	32.2 (3.32)	16.8 (0.49)
45–64	21.5 (0.63)	28.2 (1.95)	20.7 (0.62)
≥65	16.9 (0.58)	20.5 (1.45)	16.1 (0.68)
Sex			
Men	16.2 (0.50)	17.8 (1.38)	16.1 (0.51)
Women	21.4 (0.52)	33.1 (1.69)	20.1 (0.53)
Race/ethnicity			
Non-Hispanic white	18.4 (0.43)	26.7 (1.79)	17.7 (0.45)
Non-Hispanic black	18.8 (0.70)	21.1 (1.51)	18.4 (0.74)
All Hispanic	24.2 (0.74)	26.9 (1.88)	23.9 (0.85)
Mexican American	24.1 (0.80)	25.7 (2.31)	24.1 (0.85)

Diabetes is defined as self-reported health care provider diagnosis. Nonalcoholic fatty liver disease is defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma glutamyltransferase (GGT) greater than the 95th percentile in adults at low risk for liver injury, excluding heavy drinkers (>2 drinks/day for men or >1 drink/day for women) and those with viral hepatitis (positive serum markers of hepatitis B or C). Data are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years.

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

pressure, elevated fasting glucose level, or BMI ≥25 kg/m² used as an index of obesity in Asians in place of abdominal obesity (34).) Furthermore, those with NAFLD and the metabolic syndrome at baseline were less likely to have remission of NAFLD than those without the metabolic syndrome (adjusted OR 0.47, 95% CI 0.26–0.85 for men and OR 0.47, 95% CI 0.26–0.84 for women). In another cohort study of workers in Japan, followed for a median of 5 years, NAFLD defined by elevated liver enzymes developed in 14.7% of adults age 20–39 years and 8.1% of those age 40–59 years (32). While there were no associations in the younger age group (perhaps due to smaller sample size), diabetes or glucose intolerance was the only predictor of incident NAFLD, increasing the risk over fourfold (HR 4.2, 95% CI 1.1–15.7) in the older age group.

Determining the directionality of the association of diabetes and NAFLD has proven difficult for several reasons. First, the preclinical stages of both diseases make it difficult to determine the exact time each condition occurred. This is further complicated by the fact that, in clinical practice, individuals are not routinely screened for both at the same time. In research, most studies have not employed the gold standard tests for both conditions (e.g., fasting glucose, A1c, and/or oral glucose tolerance testing [OGTT], along with liver biopsy or comprehensive serologic or imaging tests that also rule out other causes), and even fewer have done this prospectively in defined cohorts.

PROGRESSION OF NAFLD

In cross-sectional studies, persons with diabetes have a significantly higher prevalence of NASH and advanced fibrosis/cirrhosis (35,36). In the few prospective studies that examined the progression of liver disease, the presence of NASH was the strongest predictor of progression (14). However, no study has clearly isolated the impact of diabetes on progression independently of other factors, including baseline histology. As mentioned, NAFLD is also known to precede HCC. While prospective data are also limited for this outcome, a number of studies have found that individuals with diabetes are at higher risk for developing HCC with relative risks of twofold to threefold for HCC compared to those without diabetes (37).

TABLE 26.4. Age-Standardized Prevalence of Presumed Nonalcoholic Fatty Liver Disease Among Persons With Diabetes, by Use of Different Diabetes Medications, U.S., 1988–1994 and 1999–2010

DIABETES MEDICATIONS	PERCENT (STANDARD ERROR)		
	Hepatic Steatosis*	Fatty Liver Index†	Elevated Liver Enzymes‡
Biguanides			
Yes		76.4§ (2.84)	25.1 (1.63)
No		64.8 (2.88)	26.1 (1.61)
Thiazolidinediones			
Yes		78.5§ (3.75)	20.6§ (2.76)
No		69.5 (2.29)	27.1 (1.30)
Sulfonylureas			
Yes	57.3§ (3.76)	75.2§ (2.83)	27.5 (1.58)
No	36.8 (4.38)	67.9 (2.34)	24.9 (1.46)
Insulin			
Yes	35.8§ (4.03)	73.4 (4.14)	27.5 (2.55)
No	49.1 (3.68)	70.5 (2.22)	25.4 (1.34)

Diabetes is defined as self-reported health care provider diagnosis. Data from 1988–1994 are standardized to the National Health Interview Survey 1991 diabetic population age 20–74 years using age categories 20–44, 45–64, and 65–74 years. Data from 1999–2010 are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years.

* Moderate-severe hepatic steatosis on abdominal ultrasound in NHANES 1988–1994, excluding heavy drinkers (>2 drinks/day for men or >1 drink/day for women).

† Fatty Liver Index ≥60 in NHANES 1999–2010, excluding heavy drinkers and those with viral hepatitis (positive serum markers of hepatitis B or C). The Fatty Liver Index = $(e^{0.953*\log e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e(\text{ggt}) + 0.053*\text{waist circumference} - 15.745}) / (1 + e^{0.953*\log e(\text{triglycerides}) + 0.139*\text{BMI} + 0.718*\log e(\text{ggt}) + 0.053*\text{waist circumference} - 15.745}) * 100$, where GGT is gamma glutamyltransferase and BMI is body mass index.

‡ Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma glutamyltransferase (GGT) greater than the 95th percentile in adults at low risk for liver injury in NHANES 1999–2010, excluding heavy drinkers and those with viral hepatitis.

§ $p<0.05$ compared with persons with diabetes not taking the medication

SOURCE: National Health and Nutrition Examination Surveys (NHANES) 1988–1994 and 1999–2010

NAFLD, TYPE 2 DIABETES, AND MORTALITY

NAFLD leads to end-stage liver disease (cirrhosis) and HCC, two conditions that are strongly associated with liver-related mortality. Indeed, some studies have shown an increase in liver-related mortality in patients with NAFLD (38). Several prior population-based studies reported increased liver-related mortality in those with diabetes. As shown in Table 26.5, NAFLD is associated with increased liver-related mortality in most, but not all studies, with hazard ratios ranging from 0.64 to 13.0 compared to those without NAFLD (39,40,41,42). The Verona Diabetes Study found a standardized mortality ratio (SMR) for liver disease and cirrhosis of 2.5 (95% CI 2.0–3.2) in those with diabetes compared to the general population (43). This increased risk was slightly higher in men (SMR 2.82, 95% CI 2.08–3.76) than women (SMR 2.04, 95% CI 1.26–3.12). A study done in individuals with diabetes in Wisconsin had similar findings (SMR 2.3, 95% CI 0.9–4.7), but the results were not statistically significant, perhaps due to a small number of liver-related deaths (44). Neither of these studies determined the underlying liver disease that caused cirrhosis or liver-related mortality.

In addition to liver-related mortality, NAFLD may be associated with an increased risk of all-cause or cardiovascular mortality; however, data supporting this hypothesis are weak. In particular, population-based studies in the United States have shown mixed results (Table 26.5). As with prevalence studies, the diagnostic criteria for NAFLD in these studies have differed substantially. In general, studies using liver enzymes have shown a small, statistically significant risk of all-cause mortality. The highest risk has been shown in those with elevations in GGT. Using ultrasound to identify NAFLD

TABLE 26.5. Population-Based Studies of Nonalcoholic Fatty Liver Disease and Mortality in the United States

POPULATION, YEARS (REF.)	MEASURE OF NAFLD	N WITH NAFLD	FOLLOW-UP (YEARS)	RISK* (95% CONFIDENCE INTERVAL)				ADJUSTMENTS
				All-Cause Mortality	All-Cause Mortality in Those With Diabetes	Cardiovascular Mortality	Liver-Related Mortality	
NHANES III, 1988–2000 (39)	ALT	980	8.7 (mean)	Age 45–54 years: 4.14 (1.26–13.58) Age 55–84 years: 1.26 (0.76–2.06)		Age 45–54 years: 8.43 (2.43–22.72) Age 55–84 years: 0.79 (0.28–2.19)	4.15† (0.55–31.11)	Age, sex, race/ethnicity, systolic blood pressure, diastolic blood pressure, waist circumference, total cholesterol, HDL cholesterol, triglyceride, smoking, CRP, daily alcohol, physical activity, diabetes, HMG-CoA reductase inhibitor use
NHANES III, 1988–2000 (40)	ALT	2,156	8.8 (median)	1.2 (0.88–1.60)		0.90 (0.56–1.4)	8.2 (2.1–31.9)	Age, sex, race/ethnicity, BMI, waist-to-hip ratio, glucose status, total cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, CRP, transferrin saturation, education
NHANES III, 1988–2000 (40)	GGT	1,998	8.8 (median)	1.5 (1.2–1.8)		1.3 (0.8–2.0)	13.0 (2.4–71.5)	Age, sex, race/ethnicity, BMI, waist-to-hip ratio, glucose status, total cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, CRP, transferrin saturation, education
NHANES III, 1988–2006 (41)	Ultrasound	2,089	14.5 (median)	0.92 (0.76–1.09)	0.79‡ (0.58–1.07)	0.86 (0.67–1.12)	0.64 (0.12–3.59) 1.17§ (0.15–8.93)	Age, sex, race/ethnicity, education, smoking, alcohol, physical activity, BMI, hypertension, hypercholesterolemia, diabetes
Italian adults with diabetes, 2000–2006 (42)	Ultrasound	384	6.5 (mean)			1.87 (1.2–2.6)		Age, sex, smoking history, diabetes duration, A1c, LDL cholesterol, GGT levels, use of medications, the metabolic syndrome

A1c, glycosylated hemoglobin; ALT, alanine aminotransferase; BMI, body mass index; CRP, C-reactive protein; GGT, gamma glutamyltransferase; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey.

* Risk for all mortality categories is estimated by hazard ratios, except Reference 42, where an odds ratio is presented.

† Age-standardized (to the 2000 U.S. population age 35–84 years) mortality rate; unadjusted.

‡ P for interaction by diabetes status=0.24

§ Hazard ratio for those with steatosis on ultrasound and elevated liver enzymes

SOURCE: References are listed within the table.

in the NHANES III, there was no increased risk of all-cause mortality overall and no difference in risk in those with NAFLD and diabetes compared to those with NAFLD and no diabetes (p=0.24) (Table 26.5) (41). A population-based study in Minnesota found an increase in all-cause mortality among those with NAFLD compared to the general population (SMR 1.55, 95% CI 1.11–2.11) (45). Those with diabetes also had a significant increase in all-cause mortality, independent of NAFLD; however, no test for interaction was reported.

Finally, another analysis of the NHANES III found that an elevation in GGT was associated with increased risk of diabetes-related mortality (HR 3.3, 95% CI 1.4–7.6) even after adjustment for multiple factors, but elevated ALT was not associated with diabetes mortality (40). Because most studies have not reported on diabetes-related mortality, this finding remains to be replicated.

NAFLD is associated with increased liver-related mortality, as well as all-cause mortality, but limited data suggest that this does not differ in people with diabetes compared to those without. NAFLD may be associated with increased cardiovascular mortality, especially in older adults and in those with diabetes, but these findings require verification. Future studies are needed to assess the prognostic implications of different stages of liver disease in people with diabetes on all-cause, cardiovascular, and cancer mortality.

VIRAL HEPATITIS

HEPATITIS C AND DIABETES

In the United States, chronic HCV is the leading indication for liver transplantation and the leading cause of death from liver disease (46,47,48). The presence of IgG antibody to the virus (anti-HCV) in the blood indicates either past or current infection. A positive blood test for HCV RNA indicates ongoing infection. An association between HCV and type 2 diabetes has been noted beginning shortly after the discovery of HCV in 1989. Subsequently, a meta-analysis found diabetes to be more frequent among persons with HCV with an adjusted odds ratio of 1.68 based on seven cross-sectional studies and a hazard ratio of 1.67 based on three cohort studies (49). However, many of these studies were clinical series, in which ascertainment bias is likely because patients under medical care for one chronic condition (such as diabetes) are more likely to undergo testing for other chronic diseases (such as HCV), especially if they have features in common, such as elevated liver enzyme activity (50). Published population-based studies and other cohort studies that avoided ascertainment bias demonstrated a moderate association of the two conditions, but the results have not been consistent (see below). In addition, patients with HCV are likely to have advanced liver disease, which may increase the risk of diabetes independently of cause. This concern may be somewhat mitigated in studies that include liver biopsies or that compare diabetes in HCV versus other causes of chronic liver disease.

The association between diabetes and HCV has been specifically examined in four population-based studies without consistent results (51,52,53,54). In the NHANES III, a nonstatistically significant association was found between the presence of anti-HCV antibody and diabetes that was either self-reported or detected by glucose tolerance testing (51). A stronger association was found when analysis was restricted to participants age ≥40 years (adjusted OR 3.77, 95% CI 1.80–7.87), but it was not clear why the association was found in only one age group. In the Atherosclerosis Risk in Communities Study (ARIC), persons free of diabetes (determined by self-report or fasting plasma glucose) had three subsequent visits over approximately 10 years (52). In a modified nested case-control study, samples from baseline visits were subsequently tested for anti-HCV antibody. Overall, a nonstatistically significant association of HCV and subsequent diabetes was found with a relative hazard of 1.9 (95% CI 0.6–6.2). However, an increased relative hazard was found for participants at high risk of diabetes (based on age and BMI) of 11.6 (95% CI 1.4–96.6). This finding was based on only eight anti-HCV positive cases. For the low-risk group, the relative hazard was 0.48 (95% CI 0.05–4.4), based on seven anti-HCV positive participants. Among obese participants only, insulin levels were higher at baseline in the anti-HCV positive group. The strongest population-based evidence for an increased risk of diabetes with HCV has come from a Taiwanese community-based cohort (53). Nearly 5,000 persons age ≥40 years without diabetes (diabetes was defined as fasting plasma glucose ≥126 mg/dL or casual glucose ≥200 mg/dL [≥11.10 mmol/L]) were followed for 7 years. At baseline, 812 participants were anti-HCV positive, 544 positive for HBsAg, and 116 positive for both. Cumulative incidence of diabetes was 8.6% for seronegative individuals, 14.3% for anti-HCV positive alone, and 7.5% for HBsAg positive alone. The adjusted hazard ratio for diabetes if anti-HCV positive was 1.7 (95% CI 1.3–2.8). The association was strongest in persons of younger age or higher BMI. In contrast, a cohort study from Italy found no association between baseline anti-HCV positivity and subsequent development of diabetes in multivariate analysis (OR 0.65, 95% CI 0.41–1.04) (54).

In analysis for *Diabetes in America*, of the cross-sectional, population-based NHANES 1999–2010, among nearly 29,000 tested participants, 566 were anti-HCV positive and 393 were HCV RNA positive. The diagnosis of diabetes was based on self-report, A1c ≥6.5%, or fasting glucose ≥126 mg/dL. Prediabetes was defined as A1c 5.7%–6.4% or fasting glucose 100–125 mg/dL. The definition of normal glucose levels required both an A1c <5.7% and a fasting plasma glucose <100 mg/dL.

TABLE 26.6. Age-Standardized Prevalence and Odds Ratios of Positive Serum Antibody to Hepatitis C Virus (HCV Ab+), by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2010

	DIABETES		PREDIABETES		NORMAL GLUCOSE
CHARACTERISTICS	Percent (95% CI)	OR* (95% CI)	Percent (95% CI)	OR* (95% CI)	Percent (95% CI)
Total	1.6 (1.2–2.2)	0.8 (0.5–1.5)	1.8 (1.3–2.4)	1.0 (0.7–1.5)	1.8 (1.3–2.6)
Age (years)					
20–44	2.8 (1.1–7.1)	1.8 (0.6–5.1)	1.3 (0.7–2.2)	0.9 (0.5–1.7)	1.1 (0.7–1.6)
45–64	2.0 (1.4–2.9)	0.8 (0.5–1.4)	3.1 (2.2–4.3)	1.1 (0.7–1.9)	2.9 (2.1–4.1)
≥65	0.7 (0.4–1.1)	1.0 (0.2–4.0)	0.4 (0.2–0.8)	0.5 (0.1–2.5)	0.8 (0.2–3.3)
Sex					
Men	1.6 (1.0–2.4)	0.7 (0.3–1.4)	2.5 (1.8–3.6)	1.1 (0.7–1.9)	2.3 (1.5–3.4)
Women	1.6 (1.0–2.6)	1.3 (0.6–2.9)	0.8 (0.5–1.4)	0.8 (0.5–1.4)	1.5 (0.8–2.6)
Race/ethnicity					
Non-Hispanic white	1.3 (0.7–2.5)	1.0 (0.5–2.3)	1.5 (1.0–2.3)	1.3 (0.7–2.2)	1.4 (0.9–2.0)
Non-Hispanic black	4.1 (3.0–5.6)	0.9 (0.5–1.6)	3.8 (2.5–6.0)	1.0 (0.6–1.8)	3.7 (2.4–5.6)
Mexican American	1.7 (0.9–2.9)	0.5 (0.2–1.1)	1.8 (1.1–3.1)	0.7 (0.3–1.4)	2.1 (1.2–3.9)
Other	0.7 (0.3–1.9)	0.2 (0.0–1.3)	2.0 (0.9–4.4)	0.9 (0.2–4.2)	6.4 (1.7–20.8)

Diabetes is defined as self-reported health care provider diagnosis or glycosylated hemoglobin (A1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL. Prediabetes is defined as A1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dL; normal glucose is defined as A1c <5.7% and fasting plasma glucose <100 mg/dL. Data are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. CI, confidence interval; OR, odds ratio.

* Normal glucose is the reference group. Odds ratios for the total population are adjusted for age, sex, and race/ethnicity.

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

The prevalence of anti-HCV was similar across glucose categories, both overall and by demographic subgroups (Table 26.6). The age-sex-race/ethnicity adjusted odds ratios for anti-HCV positive were not increased for either diabetes (OR 0.8) or prediabetes (OR 1.0) relative to normal glucose levels. Similarly, the prevalence of HCV RNA positivity was not different across glucose categories, and the adjusted odds ratios were not higher for diabetes and prediabetes (Table 26.7). The overall results for anti-HCV and HCV RNA are summarized in Figure 26.2. Diabetes and prediabetes remained unassociated with HCV infection in multivariate analyses that adjusted for additional factors (55).

A finding of increased insulin resistance among persons with HCV would strengthen the evidence for an association of diabetes. Surrogate estimates for increased insulin resistance, such as high homeostasis model assessment of insulin resistance (HOMA-IR), have been found more commonly among persons with HCV than those without (56,57,58). Stronger evidence of a relationship of HCV to insulin resistance comes from HCV treatment studies in which glucose and insulin were measured before and after treatment. Improvement in insulin resistance among treated patients who clear virus (i.e., achieve a sustained virologic response) relative to patients who do not clear the virus would provide support for the hypothesis that chronic HCV infection has a direct effect on glucose dysregulation. Most studies of HCV and insulin resistance used HOMA-IR to estimate insulin resistance (59). In general, a decline was seen in estimated insulin resistance among those who achieved a sustained virologic response that did not occur among patients who were nonresponders to treatment or who had virologic relapse following treatment (60,61,62,63). However, concerns have been raised about the accuracy of HOMA-IR and other surrogate measures of insulin resistance in chronic HCV (64). One small study utilized a more direct measure of insulin resistance—insulin suppression tests (65). The authors found a nonstatistically significant greater improvement in insulin resistance among 14 patients with sustained virologic response than among nine nonresponders (65). At least two studies with longer-term follow-up indicated a lower risk of new-onset diabetes among participants who achieved a sustained virologic response (66,67). It should be noted that an improvement in insulin resistance among patients with sustained virologic response might not be a direct effect of virus elimination. It could also be due to improvement in liver function following virus eradication (68).

In conclusion, it is possible that HCV has a permissive rather than direct effect on the development of diabetes. Thus, HCV may act in concert with other determinants to increase the risk of diabetes.

TABLE 26.7. Age-Standardized Prevalence and Odds Ratios of Presence of Serum Hepatitis C Virus RNA, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2010

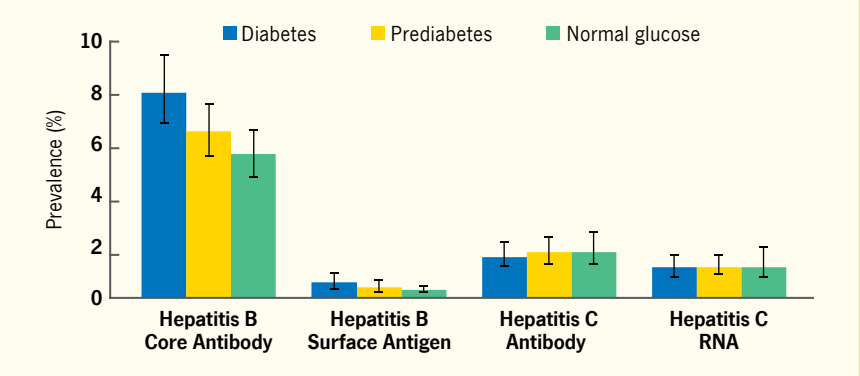
CHARACTERISTICS	DIABETES		PREDIABETES		NORMAL GLUCOSE
	Percent (95% CI)	OR* (95% CI)	Percent (95% CI)	OR* (95% CI)	Percent (95% CI)
Total	1.2 (0.8–1.7)	0.9 (0.4–1.8)	1.2 (0.9–1.7)	1.1 (0.7–1.7)	1.2 (0.8–2.0)
Age (years)					
20–44	2.3 (0.9–6.1)	3.0 (1.0–9.3)	0.8 (0.4–1.6)	1.3 (0.6–2.6)	0.5 (0.3–0.7)
45–64	1.5 (1.0–2.3)	0.9 (0.5–1.6)	2.2 (1.6–3.2)	1.2 (0.7–2.1)	2.0 (1.3–2.9)
≥65	0.5 (0.2–0.9)	0.8 (0.2–4.3)	0.3 (0.1–0.7)	0.4 (0.1–3.1)	0.6 (0.1–3.6)
Sex					
Men	1.4 (0.9–2.2)	0.9 (0.4–1.8)	1.8 (1.2–2.5)	1.1 (0.6–2.0)	1.7 (1.0–2.7)
Women	1.0 (0.6–1.8)	1.5 (0.5–4.1)	0.6 (0.4–1.1)	1.2 (0.6–2.3)	0.9 (0.4–2.2)
Race/ethnicity					
Non-Hispanic white	1.1 (0.5–2.1)	1.6 (0.7–3.7)	1.0 (0.6–1.6)	1.7 (0.9–3.3)	0.8 (0.5–1.3)
Non-Hispanic black	3.1 (2.1–4.5)	1.0 (0.5–2.0)	3.4 (2.1–5.5)	1.3 (0.7–2.4)	2.6 (1.5–4.4)
Mexican American	0.9 (0.4–2.0)	0.5 (0.2–1.3)	0.8 (0.3–1.9)	0.3 (0.1–0.9)	1.5 (0.7–3.0)
Other	0.4 (0.1–1.0)	0.1 (0.0–0.8)	1.4 (0.5–3.4)	0.6 (0.1–3.5)	6.0 (1.5–21.0)

Diabetes is defined as self-reported health care provider diagnosis or glycosylated hemoglobin (A1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL. Prediabetes is defined as A1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dL; normal glucose is defined as A1c <5.7% and fasting plasma glucose <100 mg/dL. Data are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* CI, confidence interval; OR, odds ratio; RNA, ribonucleic acid.

* Normal glucose is the reference group. Odds ratios for the total population are adjusted for age, sex, and race/ethnicity.

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

FIGURE 26.2. Age-Standardized Prevalence of Hepatitis B and Hepatitis C, by Diabetes Status, U.S., 1999–2010



Diabetes is defined as self-reported health care provider diagnosis or glycosylated hemoglobin (A1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL. Prediabetes is defined as A1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dL; normal glucose is defined as A1c <5.7% and fasting plasma glucose <100 mg/dL. Data are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years. Error bars represent 95% confidence intervals. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.* RNA, ribonucleic acid.

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

HEPATITIS B AND DIABETES

There are several tests for HBV infection. For epidemiologic studies, the most commonly used and useful tests are serum HBcAb, which indicates exposure to HBV, and HBsAg, which indicates current infection.

The distribution of chronic HBV infection is highly regional, being endemic throughout much of eastern Asia and parts of Africa and much less prevalent in North America and Western Europe. In the United States, HBV is a major concern among immigrants from endemic regions. Worldwide, chronic HBV infection may pose a more significant health burden than HCV. The risk of HCC is much higher in HBV than HCV, and HCC remains a leading cause of cancer mortality in much of the world.

Compared to HCV, there is less evidence that HBV increases the risk of diabetes. In fact, several studies have used patients with HBV as the reference group when examining the prevalence of diabetes in HCV (69,70,71,72). In the study from Taiwan in which HCV was shown to increase the rate of new-onset diabetes, the incidence of diabetes among participants with chronic HBV (positive for HBsAg) was not greater than among those who were HBV-seronegative (53).

New analyses of NHANES 1999–2010 data on HBV serology and diabetes were conducted for *Diabetes in America*. Among over 30,000 tested participants, 1,998 were HBcAb positive and 115 were HBsAg positive. As with the HCV analysis, the diagnosis of diabetes was based on self-report, A1c ≥6.5%, or fasting glucose ≥126 mg/dL. The unadjusted prevalence of HBcAb was higher among those participants with diabetes (8.0%) compared with participants with normal glucose levels (5.6%) (Table 26.8). This difference was more pronounced among women (8.0% with diabetes vs. 4.2% with normal glucose levels). Among the different racial/ethnic groups, prevalence was especially high for non-Hispanic blacks and highest for "other" ethnicities, mostly of Asian origin. With adjustment for age, sex, and race/ethnicity, the odds

TABLE 26.8. Age-Standardized Prevalence and Odds Ratios of Positive Serum Antibody to Hepatitis B Core Antigen (HBcAb+), by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2010

	DIABETES		PREDIABETES		NORMAL GLUCOSE
CHARACTERISTICS	Percent (95% CI)	OR* (95% CI)	Percent (95% CI)	OR* (95% CI)	Percent (95% CI)
Total	8.0 (6.8–9.5)	1.0 (0.8–1.3)	6.5 (5.5–7.6)	1.1 (0.8–1.4)	5.6 (4.7–6.6)
Age (years)					
20–44	4.4 (2.7–7.2)	1.1 (0.6–2.0)	4.7 (3.4–6.5)	1.3 (0.9–1.9)	3.4 (2.7–4.2)
45–64	9.1 (7.3–11.4)	1.4 (1.0–2.1)	7.6 (6.1–9.5)	1.2 (0.8–1.7)	6.5 (5.0–8.3)
≥65	8.0 (6.7–9.6)	1.6 (1.2–2.2)	5.8 (4.6–7.3)	1.1 (0.8–1.6)	5.3 (4.0–7.1)
Sex					
Men	8.0 (6.4–10.0)	1.1 (0.8–1.6)	8.2 (6.8–9.7)	1.2 (0.9–1.7)	7.8 (6.3–9.6)
Women	8.0 (6.4–9.8)	1.8 (1.3–2.5)	4.7 (3.7–5.9)	1.1 (0.8–1.5)	4.2 (3.2–5.5)
Race/ethnicity					
Non-Hispanic white	4.2 (3.0–5.8)	1.4 (0.9–2.2)	4.1 (3.2–5.1)	1.3 (0.9–2.0)	2.9 (2.2–3.8)
Non-Hispanic black	16.4 (14.0–19.2)	0.8 (0.6–1.1)	18.1 (15.0–21.8)	0.9 (0.7–1.3)	19.2 (15.3–23.9)
Mexican American	3.8 (2.6–5.6)	1.0 (0.5–1.9)	6.1 (4.6–8.2)	1.6 (0.9–2.9)	5.5 (3.5–8.4)
Other	23.0 (17.6–29.5)	1.0 (0.6–1.8)	16.9 (12.3–22.7)	1.0 (0.5–1.8)	24.7 (17.8–33.2)

Diabetes is defined as self-reported health care provider diagnosis or glycosylated hemoglobin (A1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL. Prediabetes is defined as A1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dL; normal glucose is defined as A1c <5.7% and fasting plasma glucose <100 mg/dL. Data are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. CI, confidence interval; OR, odds ratio.

* Normal glucose is the reference group. Odds ratios for the total population are adjusted for age, sex, and race/ethnicity.

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

TABLE 26.9. Age-Standardized Prevalence and Odds Ratios of Positive Serum Hepatitis B Virus Surface Antigen (HBsAg+), by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1999–2010

	DIABETES		PREDIABETES		NORMAL GLUCOSE
CHARACTERISTICS	Percent (95% CI)	OR* (95% CI)	Percent (95% CI)	OR* (95% CI)	Percent (95% CI)
Total	0.6 (0.3–1.0)	1.2 (0.6–2.6)	0.4 (0.2–0.7)	1.1 (0.5–2.2)	0.3 (0.2–0.5)
Age (years)					
20–44	0.5 (0.1–3.5)	1.3 (0.2–10.6)	0.5 (0.2–1.2)	1.3 (0.5–3.2)	0.4 (0.2–0.6)
45–64	0.8 (0.4–1.6)	1.6 (0.5–4.5)	0.5 (0.3–1.1)	1.1 (0.4–3.2)	0.5 (0.2–1.1)
≥65	0.3 (0.1–0.8)	6.6 (1.0–42.6)	0.1 (0.0–0.6)	2.5 (0.3–22.8)	0.1 (0.0–0.3)
Sex					
Men	0.6 (0.3–1.4)	2.3 (0.8–7.0)	0.5 (0.3–1.1)	2.0 (0.9–4.6)	0.3 (0.1–0.5)
Women	0.5 (0.2–0.9)	1.2 (0.5–2.9)	0.2 (0.1–0.5)	0.5 (0.1–1.9)	0.3 (0.1–0.8)
Race/ethnicity					
Non-Hispanic white	0.3 (0.1–1.0)	5.3 (1.0–27.8)	0.3 (0.1–0.7)	5.5 (1.1–26.6)	0.1 (0.0–0.2)
Non-Hispanic black	0.9 (0.4–1.7)	0.4 (0.2–1.1)	0.4 (0.1–0.9)	0.4 (0.1–1.1)	1.9 (1.1–3.3)
Mexican American	0.2 (0.0–1.2)	3.8 (0.1–121.0)	0.3 (0.1–1.4)	3.8 (0.3–51.5)	0.2 (0.0–1.3)
Other	1.5 (0.6–3.9)	1.4 (0.3–5.7)	0.8 (0.3–2.1)	0.9 (0.3–2.8)	1.0 (0.2–4.4)

Diabetes is defined as self-reported health care provider diagnosis or glycosylated hemoglobin (A1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL. Prediabetes is defined as A1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dL; normal glucose is defined as A1c <5.7% and fasting plasma glucose <100 mg/dL. Data are standardized to the National Health Interview Survey 2010 diabetic population age ≥20 years using age categories 20–44, 45–64, and ≥65 years. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. CI, confidence interval; OR, odds ratio.

* Normal glucose is the reference group. Odds ratios for the total population are adjusted for age, sex, and race/ethnicity.

SOURCE: National Health and Nutrition Examination Surveys 1999–2010

ratios for HBcAb were not elevated for diabetes (OR 1.0, 95% CI 0.81–1.3) and prediabetes (OR 1.1, 95% CI 0.82–1.4) relative to participants with normal glucose levels. The prevalences and odds ratios for the much smaller number of participants positive for HBsAg were not elevated for participants with diabetes or prediabetes relative to those with normal glucose levels (Table 26.9). Overall results for HBcAb and HBsAg are summarized in Figure 26.2.

DIABETES AND CIRRHOSIS

An association of diabetes and liver cirrhosis was established more than 50 years ago (73). In more recent studies of patients with cirrhosis undergoing OGTT, diabetes has been detected in a high percentage of patients with cirrhosis, ranging from 35% to as high as 71% (Table 26.10) (72,74,75,76,77,78). Among patients with chronic viral hepatitis, those with cirrhosis have a higher prevalence of diabetes than those without cirrhosis (72). Furthermore, the prevalence of diabetes increases with declining liver function among patients with cirrhosis. Investigators have differentiated diabetes mellitus (presumably type 2) from hepatogenous diabetes due to chronic liver disease, but the differentiation has been based largely on whether diabetes was recognized before (type 2) or after (hepatogenous) the diagnosis of cirrhosis and not on a pathophysiologic basis (76,79). A striking feature of diabetes associated with cirrhosis is the high proportion of patients with normal fasting glucose.

TABLE 26.10. Prevalence of Diabetes Among Patients With Cirrhosis Who Had Oral Glucose Tolerance Testing

LOCATION, YEARS (REF.)	LIVER DISEASE/ PRETESTING DIABETES STATUS	DIAGNOSIS OF DIABETES	DIABETES PREVALENCE	COMMENTS
Detmold, Germany, 1997 (74)	23 with compensated cirrhosis; 29 with decompensated cirrhosis	Previous diagnosis or 100 g 3-hour OGTT	71%	Most diagnosed on postload testing
Hannover, Germany, 1989–1990 (77)	108 without diabetic fasting glucose	OGTT (1 g/kg body weight)	37%	Child-Pugh stage of cirrhosis had little effect on diabetes prevalence.
Hannover, Germany, NR (78)	100 with normal fasting glucose	75 g OGTT (WHO)	35%	12 patients had diabetes by OGTT post-OLT; all had IGT or diabetes pre-OLT.
Palermo, Italy, NR (72)	127 HCV 38 HBV	OGTT (1 g/kg body weight)	23.6% HCV 9.4% HBV	
Porto Alegre, Brazil, NR (75)	62 patients listed for transplant, 19% with compensated liver disease; diabetes previously undiagnosed	75 g OGTT (WHO)	65%	78% were diagnosed on 2-hour sample.
Monterrey, Mexico, 2007–2010 (76)	130 with compensated cirrhosis	75 g OGTT (WHO)	40.7%	

HBV, hepatitis B virus; HCV, hepatitis C virus; IGT, impaired glucose tolerance; NR, not reported; OGTT, oral glucose tolerance test; OLT, orthotopic liver transplantation; WHO, World Health Organization.

SOURCE: References are listed within the table.

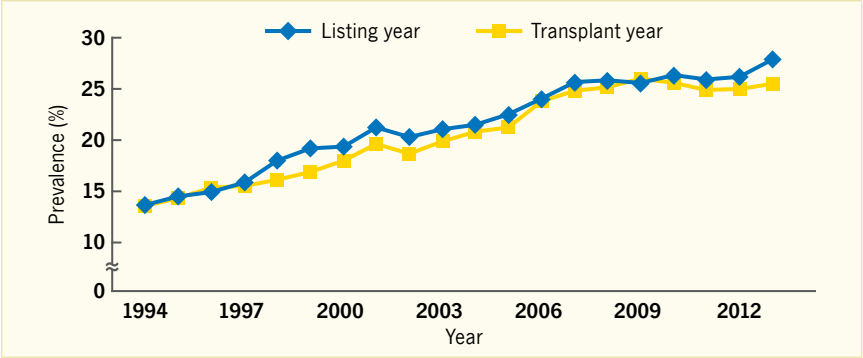
The incidence of new-onset diabetes is also high among persons with cirrhosis. In an Italian study of 100 patients with compensated cirrhosis (Child-Turcotte class A) who had normal OGTT, 21% developed diabetes during 4 years of follow-up even without overt worsening of liver function (80). The risk was higher among patients who had deteriorating liver function (35%). The presence of portal hypertension appeared to increase the risk of diabetes. Additionally, patients with cirrhosis and diabetes appear to have a worse prognosis than those with cirrhosis without diabetes (75,81).

DIABETES AND LIVER TRANSPLANTATION

The large majority of adult liver transplantation is performed for decompensated cirrhosis and for HCC. Most patients with HCC also have cirrhosis, but not necessarily advanced enough to trigger the need for transplantation on its own.

Data on all patients listed for liver transplantation in the United States from the SRTR SAF have been newly analyzed for *Diabetes in America*. There has been a steady increase in the recognition of diabetes at the time of listing since it was first recorded as a comorbidity in listed patients (Figure 26.3). From 1994, when 13.7% (n=507) of listed patients carried a diagnosis of diabetes, the proportion doubled to 27.9% in 2013 (n=2,321). Although this doubling in prevalence is striking, it is difficult to interpret. As stated, a high proportion of patients with cirrhosis are found to have diabetes when specifically tested for it. Thus, the observed increase might be due to a combination of an actual increase in diabetes and an increase in its diagnosis. Characteristics of patients with and without diagnosis of diabetes at the time of listing and at transplantation are shown in Table 26.11. Patients with diabetes were more likely to be older, male, Hispanic, less educated, have poorer functional status, on dialysis, hypertensive, and have higher BMI than those without diabetes. Interestingly, Model for End-Stage Liver Disease (MELD) scores (a scale used for prioritizing liver transplant candidates in which a higher score indicates a more urgent need within the next 3 months)

FIGURE 26.3. Prevalence of Diabetes Among Adult Liver Transplant Candidates, by Listing and Transplant Year, U.S., 1994–2013



SOURCE: Standard Analysis File of the Scientific Registry of Transplant Recipients 1994–2013

TABLE 26.11. Characteristics of Adult Patients at Listing for Liver Transplantation and at Transplantation, by Diabetes Status, U.S., 1994–2013

AT LISTING	N	DIABETES (N=33,078)	NO DIABETES (N=116,102)	P-VALUE*
Age (years; mean (SD))	149,180	56.3 (8.4)	51.6 (10.6)	<0.001
Male (%)	94,597	64.6	63.1	<0.001
Ethnicity (%)				<0.001
White	108,559	67.8	74.2	
Black	12,208	8.5	8.1	
Hispanic	20,469	17.7	12.6	
Asian	6,352	4.7	4.1	
Other (non-missing)	1,592	1.3	1.0	
Highest education level (≥associate degree; %)	25,595	21.2	22.2	<0.001
Functional status (needs assistance; %)	59,666	49.2	44.3	<0.001
Liver disease diagnoses (%)†				
Hepatitis C	60,184	37.2	41.2	<0.001
Alcoholic liver disease	41,601	23.8	29.0	<0.001
Autoimmune or cholestatic	19,047	7.8	14.2	<0.001
Hepatocellular carcinoma	17,251	14.3	10.8	<0.001
Other causes of cirrhosis	14,847	16.0	8.2	<0.001
Hepatitis B	6,461	3.8	4.5	<0.001
Fatty liver	7,482	13.1	2.7	<0.001
BMI (kg/m^2; mean (SD))	146,694	29.7 (5.9)	27.9 (5.7)	<0.001
MELD score (beginning 2/28/02), mean (SD)	113,378	16.3 (7.9)	17.4 (8.7)	<0.001
Kidney dialysis (%)	5,541	5.8	3.6	<0.001
Drug-treated hypertension (%)	26,270	36.2	15.4	<0.001
Blood type O (%)	69,016	46.4	46.2	0.62
AT TRANSPLANT	**N**	**DIABETES (N=17,958)**	**NO DIABETES (N=65,528)**	**P-VALUE***
Time on waiting list (days; mean (SD))	83,486	257 (411)	259 (441)	0.68
Functional status (needs assistance; %)	39,454	62.9	57.5	<0.001
Cold ischemia time (minutes; mean (SD))	75,947	7.4 (3.8)	7.4 (3.8)	0.039
MELD score (beginning 2/28/02), mean (SD)	54,237	17.5 (8.4)	18.7 (8.9)	<0.001
Variceal bleeding (%)	1,912	6.1	5.7	0.28
Donor characteristics				
Age (years; mean (SD))	83,481	41.1 (17.3)	39.6 (17.0)	<0.001
Male (%)	49,698	59.7	59.5	0.61
Ethnicity (%)				<0.001
White	59,059	69.4	71.1	
Black	12,256	15.7	14.4	
Hispanic	9,698	11.7	11.6	
Asian	1,797	2.4	2.1	
Other (non-missing)	649	0.8	0.8	

BMI, body mass index; MELD, Model for End-Stage Liver Disease; SD, standard deviation.
* From a t-test for means or χ^2 test for percentages.
† Because patients may have more than one liver disease, the percentages are not mutually exclusive and add to greater than 100%.

SOURCE: Standard Analysis File of the Scientific Registry of Transplant Recipients 1994–2013

were lower among patients with diabetes (mean 16.3) than among patients without known diabetes (mean 17.4). At the time of transplant, a higher MELD score among those without diabetes was still present. Diabetic patients received livers from donors who were slightly older and less likely to be of white race compared with donors of nondiabetic patients. Table 26.11 shows the percentages of patients with a given liver disease by diabetes status. For example, an HCV diagnosis was present among 37.2% of 33,078 listed patients with diabetes and 41.2% of 116,102 listed patients without diabetes. Because patients may have more than one liver disease, the percentages are not mutually exclusive and add to greater than 100%. Regarding the association of diabetes with liver disease diagnosis, it may be more informative to consider the proportion listed with diabetes according to liver disease diagnosis:

- 58.0% for fatty liver
- 35.7% for other causes of cirrhosis
- 27.3% for HCC
- 20.4% for HCV
- 19.5% for HBV
- 19.0% for alcoholic liver disease
- 13.6% for autoimmune liver disease

The high percentage for fatty liver is not surprising, given the strong association of fatty liver with diabetes (see the section *Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis*). A high proportion of those patients with "other causes of cirrhosis" probably also had fatty liver, because the diagnosis has only recently received attention and because the amount of fat declines with advanced cirrhosis and may be difficult to detect. Because diabetes is a risk factor for HCC, the high percentage of cancer cases with diabetes is not surprising. It is noteworthy that the recognition of diabetes among patients with HCV was just modestly higher than for HBV, which as noted, has not been considered to connote as high a risk of diabetes as HCV.

Between the time of listing and transplantation, transplant candidates with diabetes are more likely to die or to be withdrawn from the waiting list, usually

because of deteriorating health. These events occurred among 25.8% of those with diabetes and 22.2% of those without diabetes. The odds ratio for death or withdrawal from the waiting list was 1.22 (95% CI 1.19–1.26). Due to this increased risk of death or withdrawal, the proportion of patients with diabetes at the time of transplantation has been slightly less than at listing but has increased just as quickly over time (Figure 26.3).

Diabetes is frequently recognized following liver transplantation regardless of the cause of liver disease due, at least in part, to immunosuppression posttransplantation. It has been suggested that the risk of posttransplant diabetes is greater among patients transplanted for HCV. In a meta-analysis of seven studies, the overall risk of posttransplant diabetes was 37.5% among HCV negative patients and 53.7% among patients who were HCV positive (82). The summary odds ratio was 2.5 (95% CI 1.4–4.2). A 2010 analysis of SRTR data reported that 28.8% of HCV infected recipients and 23.7% of uninfected recipients developed new-onset diabetes over a median follow-up of 685 days (83). The multivariate-adjusted hazard ratio was modest: 1.15 (95% CI 1.07–1.24) for infected versus uninfected patients. Risk factors for development of diabetes for both infected and uninfected patients included older age, higher BMI, the use of tacrolimus and steroid in the immunosuppression regimen, and lack of immunosuppression induction. Posttransplant HCV infection also has a modest association with insulin resistance (84,85). The increased posttransplant risk of diabetes with HCV could be due to a specific diabetogenic effect of HCV. Because liver disease is often accelerated due to the nearly universal posttransplant recurrence of HCV, liver function may have already deteriorated by the time of evaluation for diabetes. In contrast, many other liver diseases do not recur following transplantation or their evolution is slow. Furthermore, none of the analyses of "new-onset" posttransplant diabetes included pretransplant OGTT (86,87,88,89,90,91,92,93). The few studies that have diagnosed diabetes based on OGTT found that a high proportion of those with diabetes after transplant had impaired glucose tolerance or diabetes (as diagnosed by the 2-hour postload plasma glucose) before transplant (78,94).

GALLBLADDER DISEASE

Gallstone disease is a common condition affecting more than 20 million adults in the United States (95). The majority of gallstones in the United States are composed primarily of cholesterol. Cholesterol gallstones are believed to develop as a result of three factors: (1) a higher proportion of cholesterol relative to solubilizing bile acids and phospholipids in bile, (2) a higher proportion of pronucleating factors relative to antinucleating factors in bile, and (3) impaired gallbladder motility, which increases the opportunity for cholesterol nucleation in the gallbladder. Abdominal ultrasonography is the criterion standard for diagnosis of gallstones because of its accuracy and safety. The majority of gallstones remain asymptomatic. For symptomatic gallstones, the primary treatment is cholecystectomy (surgical removal of the gallbladder), the majority of which are performed laparoscopically. Gallstone disease can be defined as the presence of gallstones on ultrasound or a history of a cholecystectomy. Established risk factors are older age, female sex, overweight and obesity, higher parity, and family history. Other factors that have been associated with a higher prevalence of gallstone disease are American Indian and, among women, Mexican American ethnicities, rapid weight loss, central adiposity, and cigarette smoking, while a lower prevalence of gallstones has been found in association with non-Hispanic black and some Asian race ethnicities, higher alcohol consumption, and greater physical activity.

GALLSTONE DISEASE AND DIABETES

The relationship between diabetes and gallstone disease is complicated by their shared risk factors, such as age and obesity. Table 26.12 summarizes studies of the relationship of gallstone disease with diabetes that have been published since *Diabetes in America, 2nd edition* (96). All listed studies are population-based and, therefore, did not suffer from the ascertainment bias that can occur with selected patient samples. In all studies, gallstone disease was identified using ultrasonography. Diabetes was variably defined based on a self-reported health care provider diagnosis, fasting plasma glucose, or an OGTT.

In the general U.S. population, both men and women reporting a diagnosis of diabetes were over 50% more likely to have gallstone disease compared to persons without a diabetes diagnosis after adjustment for multiple shared risk factors (Table 26.12) (95). Men and women with undiagnosed diabetes (fasting plasma glucose ≥126 mg/dL) were approximately twice as likely to have gallstone disease as persons with normal fasting glucose (<110 mg/dL [<6.11 mmol/L]) (Table 26.12) (97). This relationship reached statistical significance only among women. Impaired fasting glucose (110–125 mg/dL) was unrelated to gallstone disease among either women or men. Two other studies were conducted in the United States. Among Mexican Americans in a Texas county, women with previously diagnosed diabetes who were receiving treatment, or with newly identified diabetes based on two fasting plasma glucose levels ≥120 mg/dL (≥6.66 mmol/L), were twice as likely to have gallstone disease (98), while there was no relationship among men. Among a diverse group of American Indians, women with diabetes (based on an OGTT) had an over 40% higher prevalence of gallstone disease. Among men, the odds ratio was nearly as high (OR 1.29) but did not reach statistical significance (99). These results differ from a much earlier study of Pima Indians using cholecystography to identify gallstone disease that did not find a higher prevalence among those with diabetes (100).

TABLE 26.12. Prevalence and Relative Risk of Ultrasound-Diagnosed Gallstone Disease, by Diabetes Status

POPULATION, YEARS (REF.)	DIABETES STATUS	SAMPLE SIZE	GALLSTONE DISEASE (%)	ADJUSTED OR (95% CI)
Studies of gallstone disease prevalence				
NHANES III, 1988–1994 (95)	Men	5,257		
	Diagnosed diabetes			1.54 (1.03–2.30)
	No diabetes			1.0
	Women	5,384		
	Diagnosed diabetes			1.63 (1.12–2.36)
	No diabetes			1.0
NHANES III, 1988–1994 (97)	Fasting plasma glucose (mg/dL)			
	Men			
	≥126	111	24.8	2.11 (0.76–5.85)
	≥110–125	280	10.4	0.68 (0.29–1.62)
	<110	2,281	6.9	1.0
	Women			
	≥126	109	42.6	1.91 (1.29–2.83)
	≥110–125	199	30.1	1.17 (0.70–1.95)
	<110	2,673	14.6	1.0
South Texas Mexican Americans age 15–74 years, 1985–1986 (98)	Men	300		
	Diabetes*			0.5 (0.1–2.4)
	No diabetes			1.0
	Women	699		
	Diabetes*			2.0 (1.1–3.6)
	No diabetes			1.0
Native Americans age ≥47 years (Strong Heart Study), 1993–1995 (99)	Men	1,251		
	Diabetes			1.29 (0.96–1.72)
	IGT			1.32 (0.89–1.96)
	Normal OGTT			1.0
	Women	2,045		
	Diabetes			1.43 (1.14–1.80)
	IGT			0.96 (0.71–1.29)
	Normal OGTT			1.0
Italians age 30–69 years, 1984–1987 (101)	Men	15,910		
	Diabetes			1.54† (1.24–1.91)
	No diabetes			1.0
	Women	13,674		
	Diabetes			1.92† (1.60–2.31)
	No diabetes			1.0
Italians age 30–69 years, 1984–1987 (102)	Men	336 cases, 336 controls		
	Diabetes			2.03 (0.99–4.2)
	IGT			NS
	Normal OGTT			1.0
	Women			
	Diabetes			3.85 (1.4–10.6)
	IGT			NS
	Normal OGTT			1.0
Japanese men age 48–59 years, 1986–1994 (105)	Men			
	Diabetes	461		1.3 (0.8–2.0)
	IGT	996		1.3 (0.9–1.8)
	Normal OGTT	5,442		1.0
Taiwanese adults, 2003–2004 (106)	Fasting plasma glucose (mg/dL)			
	Men	1,592		
	≥126		3.9	NS
	≥110–125		6.1	NS
	<110		8.9	1.0
	Women	1,741		
	≥126		4.3	2.11 (1.16–3.83)
	≥110–125		8.3	NS
	<110		13.9	1.0
Taiwanese adults, 2002 (107)	Fasting plasma glucose (mg/dL)			
	≥126	149		1.71 (1.01–2.96)
	≥110–125	132		0.96 (0.47–1.97)
	<110	2,100		1.0

Table 26.12 continues on the next page.

TABLE 26.12. (continued)

POPULATION, YEARS (REF.)	DIABETES STATUS	SAMPLE SIZE	GALLSTONE DISEASE (%)	ADJUSTED OR (95% CI)
Studies of gallstone disease incidence				
Italians age 30–69 years, 1985–1993 (109)	All	1,962		
	Diabetes			2.62 (1.21–5.66)
	No diabetes			1.0
Italians age 30–79 years, 1985–1998 (110)	Men	5,428		
	Gallstones			
	Diabetes			1.75 (1.04–2.96)
	No diabetes			1.0
	Cholecystectomy			
	Diabetes			2.72 (0.89–8.33)
	No diabetes			1.0
	Women	4,089		
	Gallstones			
	Diabetes			1.10 (0.58–2.09)
	No diabetes			1.0
	Cholecystectomy			
	Diabetes			1.00 (0.22–4.49)
	No diabetes			1.0

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* CI, confidence interval; IGT, impaired glucose tolerance; NHANES, National Health and Nutrition Examination Survey; NS, nonsignificant; OGTT, oral glucose tolerance test; OR, odds ratio.

* Diabetes is defined as diagnosed and treated or fasting whole blood glucose ≥120 mg/dL on repeat testing.

† Age-adjusted only

SOURCE: References are listed within the table.

Among non-U.S. studies, an Italian study (which was the largest population-based study of ultrasound-detected gallstones) found an association with diabetes among both men and women; however, the published results were adjusted only for age and not for additional confounders, such as BMI (101). In a nested case-control study from the same Italian population matched on age, sex, and BMI, gallstone disease and diabetes were statistically significantly associated among women (OR 3.85), while the relationship among men just missed statistical significance (OR 2.03) (102). In a Japanese study of men age 48–59 years that included data from two previous smaller studies (103,104) and additional participants, the adjusted odds ratio was 1.3 for both OGTT-detected diabetes and impaired glucose tolerance but neither reached statistical significance (105). Two Taiwanese studies defined diabetes based on fasting plasma glucose. An association was found in the first among women only (OR 2.11) (106), while in the second an over 70% higher prevalence of gallstone disease was found among diabetic men and women combined (107). An older Taiwanese study also found an association with diabetes (108).

Prospective studies of incident gallstone disease can evaluate the temporal relationship with potential disease risk factors and, therefore, provide evidence for a causal association; however, few have been conducted. Two Italian studies found positive relationships with diagnosed diabetes. In the first, during up to 7 years of follow-up, diabetes was related to incident gallstone disease with an odds ratio of 2.62 (109). In the second study, during a mean follow-up time of 8 years, a relationship was found among men, but not women. Among men, the odds ratio was 1.75 for gallstones and was even higher for cholecystectomy (OR 2.72), although the latter did not reach statistical significance (110).

To further evaluate the relationship of gallstone disease with diabetes in the general U.S. population, new analyses for *Diabetes in America* were conducted using gallbladder ultrasonography data on adults age 20–74 years from the NHANES III. In these analyses, gallstone disease prevalence and odds ratios may not be identical to previously published reports from the NHANES III due to differences in diabetes definitions and adjustment only for age (prevalence), or age, sex, and race/ethnicity. Diabetes can be defined in the NHANES III as diagnosed (self-reported health care provider diagnosis) and, among persons without a diagnosis, as undiagnosed (A1c ≥6.5% or fasting glucose ≥126 mg/dL), prediabetes (A1c 5.7%–6.4% or fasting glucose 100–125 mg/dL), or normal glucose (A1c <5.7% and fasting glucose <100 mg/dL). The prevalence (± standard error) of gallstone disease was 33.3%±2.6% among those with diagnosed diabetes, 23.3%±2.2% among those with undiagnosed diabetes, 20.8%±1.5% among those with prediabetes, and 16.7%±1.7% among those with normal glucose (Figure 26.4, Table 26.13). A similar pattern of increasing gallstone disease prevalence with greater impairment of glucose metabolism was observed among men and women; young, middle-age, and older adults; and non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. Compared with persons with normal glucose, those with diagnosed diabetes had an age-sex-race/ethnicity-adjusted odds ratio of 2.3 (95% CI 1.7–3.2) for gallstone disease. These increased odds ranged from double among Mexican Americans to triple among persons age 20–44 years. There was a trend toward an increased prevalence of gallstone disease among persons with undiagnosed diabetes in the total population (OR 1.5, 95% CI 1.0–2.1), which was statistically significant among women and non-Hispanic blacks. Individuals with prediabetes did not have a statistically

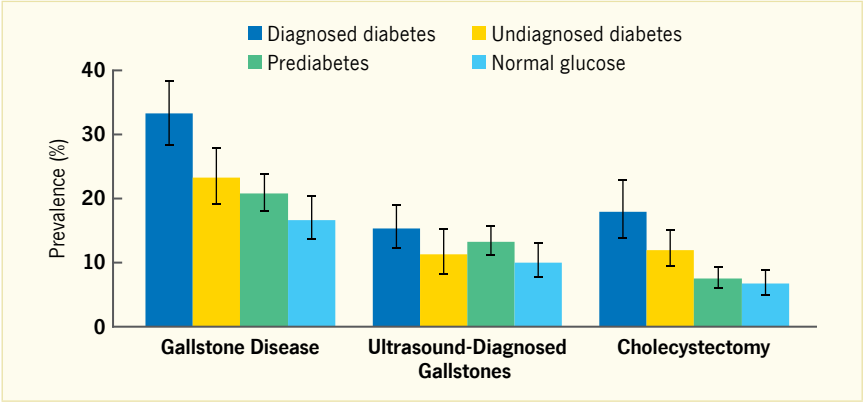
significantly higher prevalence of gallstone disease compared with those with normal glucose (OR 1.2, 95% CI 0.94–1.6), although the results were statistically significantly different among men.

When ultrasound-diagnosed gallstones and cholecystectomy were examined separately, the prevalence was higher among those diagnosed with diabetes for both gallstones (15.4%±1.7%) and cholecystectomy (17.9%±2.3%) (Figure 26.4, Table 26.13). Compared to persons with normal glucose, those with diagnosed diabetes had age-adjusted odds ratios of 1.6 (95% CI 1.1–2.4) for gallstones and 2.6 (95% CI 1.7–4.0) for cholecystectomy. Persons with undiagnosed diabetes also had a higher odds ratio for cholecystectomy (OR 1.6, 95% CI 1.1–2.5).

Similar patterns were generally seen across sex, age, and racial/ethnic subgroups, although not all relationships reached statistical significance due to smaller numbers.

Gallstone disease can be examined among those with diabetes by duration of disease and type of treatment. However, no consistent pattern was seen in the U.S. population with a longer duration or more intensive treatment of diabetes (Table 26.14).

FIGURE 26.4. Age-Standardized Prevalence of Gallstone Disease, Ultrasound-Diagnosed Gallstones, and Cholecystectomy, by Diabetes Status, U.S., 1988–1994



Diagnosed diabetes is defined as self-reported health care provider diagnosis. Undiagnosed diabetes is defined as glycosylated hemoglobin (A1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL; prediabetes is defined as A1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dL; normal glucose is defined as A1c <5.7% and fasting plasma glucose <100 mg/dL. Gallstone disease is defined as ultrasound-documented gallstones or evidence of a cholecystectomy. All gallstone disease is defined as either of these conditions. Data are standardized to the National Health Interview Survey 1991 diabetic population age 20–74 years using age categories 20–44, 45–64, and 65–74 years. Errors bars represent 95% confidence intervals. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.*

SOURCE: National Health and Nutrition Examination Survey III 1988–1994

GALLSTONE DISEASE AND INSULIN RESISTANCE

Cholesterol gallstones are associated with common metabolic abnormalities, including obesity, glucose intolerance, and dyslipidemia that are also components of the metabolic syndrome (111); hence, gallstone disease has been proposed as the gallbladder manifestation of the metabolic syndrome (112,113). The insulin resistance and hyperinsulinemia that characterize the development of type 2 diabetes play a primary role in the metabolic syndrome. Hyperinsulinemia may be more important in gallstone formation than diabetes itself (21,22,25,26,27,28,29).

TABLE 26.13. Age-Standardized Prevalence and Odds Ratios for Gallstone Disease, Ultrasound-Diagnosed Gallstones, and Cholecystectomy, by Diabetes Status, Age, Sex, and Race/Ethnicity, U.S., 1988–1994

CHARACTERISTICS/ DIABETES STATUS*	ALL GALLSTONE DISEASE		ULTRASOUND-DIAGNOSED GALLSTONES		CHOLECYSTECTOMY	
	Percent (95% CI)	OR† (95% CI)	Percent (95% CI)	OR† (95% CI)	Percent (95% CI)	OR† (95% CI)
All						
Diagnosed	33.3 (28.3–38.6)	2.3 (1.7–3.2)	15.4 (12.2–19.1)	1.6 (1.1–2.4)	17.9 (13.8–23.0)	2.6 (1.7–4.0)
Undiagnosed	23.3 (19.1–28.0)	1.5 (1.0–2.1)	11.3 (8.2–15.4)	1.2 (0.78–1.9)	12.0 (9.4–15.2)	1.6 (1.1–2.5)
Prediabetes	20.8 (17.9–24.0)	1.2 (0.94–1.6)	13.3 (11.0–15.9)	1.4 (1.0–1.9)	7.5 (5.9–9.5)	0.99 (0.65–1.5)
Normal glucose	16.7 (13.5–20.5)	1.0	10.0 (7.6–13.1)	1.0	6.7 (4.9–9.0)	1.0
Age (years)						
20–44						
Diagnosed	19.6 (10.6–33.2)	3.0 (1.4–6.4)	7.1 (3.2–15.2)	2.0 (0.74–5.6)	12.4 (5.0–27.8)	3.3 (1.2–9.1)
Undiagnosed	7.2 (4.1–12.4)	1.2 (0.59–2.6)	4.9 (2.7–8.6)	1.6 (0.70–3.5)	2.4 (0.68–7.8)	0.84 (0.23–3.1)
Prediabetes	6.5 (4.2–10.0)	0.98 (0.61–1.6)	4.6 (2.7–7.8)	1.4 (0.70–2.7)	1.9 (0.79–4.4)	0.56 (0.19–1.6)
Normal glucose	5.4 (4.1–7.1)	1.0	3.0 (2.0–4.6)	1.0	2.4 (1.6–3.4)	1.0
45–64						
Diagnosed	30.7 (24.0–38.4)	2.2 (1.4–3.5)	15.2 (11.0–20.7)	1.6 (0.97–2.8)	15.4 (10.4–22.3)	2.4 (1.5–4.1)
Undiagnosed	23.8 (17.1–32.0)	1.7 (1.0–2.6)	11.0 (6.0–19.4)	1.2 (0.60–2.4)	12.8 (8.8–18.2)	2.1 (1.2–3.9)
Prediabetes	20.8 (16.2–26.3)	1.5 (0.97–2.2)	13.0 (9.3–17.9)	1.5 (0.94–2.3)	7.8 (5.8–10.5)	1.3 (0.79–2.1)
Normal glucose	14.6 (11.0–19.1)	1.0	8.9 (6.4–12.2)	1.0	5.8 (4.0–8.2)	1.0
65–74						
Diagnosed	47.2 (39.8–54.6)	2.3 (1.6–3.3)	21.6 (15.9–28.8)	1.4 (0.79–2.3)	25.5 (19.8–32.2)	2.7 (1.6–4.6)
Undiagnosed	34.4 (24.0–46.7)	1.3 (0.72–2.5)	16.4 (9.0–28.1)	0.96 (0.42–2.2)	18.0 (11.8–26.4)	1.7 (0.91–3.4)
Prediabetes	31.3 (26.4–36.8)	1.2 (0.74–1.8)	20.1 (15.4–25.8)	1.2 (0.70–2.2)	11.2 (8.0–15.6)	1.0 (0.53–1.9)
Normal glucose	28.1 (21.4–36.0)	1.0	16.9 (11.7–23.9)	1.0	11.2 (7.2–17.0)	1.0

Table 26.13 continues on the next page.

TABLE 26.13. (continued)

CHARACTERISTICS/ DIABETES STATUS*	ALL GALLSTONE DISEASE		ULTRASOUND-DIAGNOSED GALLSTONES		CHOLECYSTECTOMY	
	Percent (95% CI)	OR† (95% CI)	Percent (95% CI)	OR† (95% CI)	Percent (95% CI)	OR† (95% CI)
Sex						
Men						
Diagnosed	23.6 (18.8–29.3)	2.6 (1.5–4.4)	16.2 (12.1–21.4)	2.3 (1.2–4.4)	7.4 (4.6–11.9)	2.7 (1.1–6.9)
Undiagnosed	17.4 (11.7–25.0)	1.6 (0.84–3.0)	10.0 (5.8–16.9)	1.2 (0.55–2.6)	7.4 (3.9–13.4)	2.7 (0.95–7.6)
Prediabetes	16.1 (12.5–20.6)	1.7 (1.1–2.5)	11.0 (8.2–14.7)	1.5 (0.92–2.4)	5.1 (3.2–8.1)	2.1 (0.75–5.7)
Normal glucose	11.6 (7.7–17.0)	1.0	8.6 (5.3–13.6)	1.0	3.0 (1.1–7.6)	1.0
Women						
Diagnosed	41.6 (34.3–49.2)	2.6 (1.8–3.8)	14.6 (10.3–20.3)	1.4 (0.85–2.2)	27.0 (20.7–34.4)	3.2 (2.0–5.2)
Undiagnosed	28.6 (22.7–35.2)	1.6 (1.1–2.4)	12.0 (8.0–17.4)	1.3 (0.80–2.3)	16.6 (12.2–22.2)	1.7 (1.1–2.8)
Prediabetes	27.1 (23.3–31.3)	1.4 (1.0–2.0)	16.5 (13.7–19.8)	1.7 (1.2–2.4)	10.6 (8.0–13.9)	1.1 (0.69–1.6)
Normal glucose	20.2 (16.2–24.9)	1.0	11.0 (8.0–14.9)	1.0	9.2 (6.7–12.4)	1.0
Race/ethnicity						
Non-Hispanic white						
Diagnosed	35.9 (29.6–42.7)	2.7 (1.9–3.8)	15.7 (12.1–20.2)	1.7 (1.1–2.6)	20.2 (14.8–26.8)	3.0 (1.9–4.9)
Undiagnosed	24.9 (19.4–31.4)	1.6 (1.0–2.4)	11.2 (7.2–16.9)	1.2 (0.66–2.1)	13.7 (10.1–18.3)	1.9 (1.1–3.3)
Prediabetes	21.4 (17.9–25.3)	1.3 (0.94–1.8)	13.7 (11.0–17.1)	1.5 (0.98–2.3)	7.6 (5.6–10.3)	1.0 (0.64–1.7)
Normal glucose	16.0 (12.9–19.6)	1.0	9.3 (7.0–12.3)	1.0	6.7 (4.8–9.2)	1.0
Non-Hispanic black						
Diagnosed	20.8 (16.4–26.0)	2.2 (1.3–3.7)	12.3 (8.9–16.7)	2.4 (1.1–5.3)	8.5 (5.5–13.0)	1.7 (0.99–2.9)
Undiagnosed	19.0 (13.8–25.6)	1.9 (1.4–2.5)	13.8 (9.2–20.1)	2.5 (1.6–3.8)	5.2 (3.0–9.1)	1.1 (0.61–1.8)
Prediabetes	11.3 (8.0–15.7)	1.1 (0.61–2.0)	6.9 (4.5–10.5)	1.3 (0.59–3.0)	4.4 (2.6–7.4)	0.82 (0.48–1.4)
Normal glucose	8.1 (4.9–13.1)	1.0	5.9 (3.1–11.0)	1.0	2.2 (1.0–4.5)	1.0
Mexican American						
Diagnosed	41.1 (36.5–45.9)	2.0 (1.3–3.1)	18.0 (13.2–24.0)	1.7 (0.97–2.9)	23.1 (17.4–30.0)	1.9 (1.2–2.9)
Undiagnosed	24.1 (15.5–35.6)	1.2 (0.64–2.4)	10.5 (5.7–18.7)	0.90 (0.41–2.0)	13.6 (7.7–22.9)	1.7 (0.85–3.5)
Prediabetes	24.2 (19.6–29.6)	1.1 (0.70–1.6)	11.2 (8.3–15.0)	1.1 (0.64–1.8)	13.0 (8.5–19.4)	1.1 (0.62–2.1)
Normal glucose	21.2 (13.0–32.6)	1.0	9.6 (4.9–18.2)	1.0	11.6 (7.6–17.2)	1.0

Gallstone disease is defined as ultrasound-documented gallstones or evidence of a cholecystectomy. All gallstone disease is defined as either of these conditions.
Data are standardized to the National Health Interview Survey 1991 diabetic population age 20–74 years using age categories 20–44, 45–64, and 65–74 years. CI, confidence interval; OR, odds ratio.

* Diagnosed diabetes is defined as self-reported health care provider diagnosis. Undiagnosed diabetes is defined as glycosylated hemoglobin (A1c) ≥6.5% or fasting plasma glucose ≥126 mg/dL; prediabetes is defined as A1c 5.7%–6.4% or fasting plasma glucose 100–125 mg/dL; normal glucose is defined as A1c <5.7% and fasting plasma glucose <100 mg/dL. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*.

† Odds ratios for the total population are adjusted for age, sex, and race/ethnicity.

SOURCE: National Health and Nutrition Examination Survey III 1988–1994

Population-based studies of the relationship between ultrasound-diagnosed gallstone disease and insulin resistance, in which an adjusted odds ratio was reported, are summarized in Table 26.15. In studies of the general population, insulin resistance has been defined either as fasting serum insulin concentration, which is typically elevated as a result of insulin resistance, or using HOMA-IR, which is calculated from fasting insulin and fasting glucose and has been validated against the criterion standard for measurement of insulin resistance, the euglycemic hyperinsulinemic clamp (114,115). In the U.S. population, among persons without a previous diabetes diagnosis, the prevalence of gallstone disease rose with increasing fasting serum insulin concentration among women, but not among men (97). The association in women was independent of multiple potential confounding factors, including fasting glucose, BMI, waist-to-hip ratio, and physical activity. However, the relationship of gallstone disease with insulin did not account for the increased risk of gallstones in persons with undiagnosed diabetes. This may have partly resulted from limitations of a cross-sectional study in which insulin levels at the time of examination may differ from those at the time of gallstone formation and limitations of using serum insulin concentration as a surrogate for insulin resistance.

TABLE 26.14. Age-Standardized Prevalence of Gallstone Disease, Ultrasound-Diagnosed Gallstones, and Cholecystectomy, by Diabetes Duration and Treatment, U.S., 1988–1994

		PERCENT (95% CONFIDENCE INTERVAL)		
	N	All Gallstone Disease	Ultrasound-Diagnosed Gallstones	Cholecystectomy
Duration (years)				
<5	383	36.2 (28.8–44.5)	16.9 (12.1–23.0)	19.4 (13.5–27.0)
5–9	191	22.9 (14.4–34.4)	11.7 (6.5–20.1)	11.2 (6.3–19.2)
10–19	247	31.2 (21.7–42.5)	13.9 (7.8–23.7)	17.2 (10.0–28.2)
≥20	141	48.3 (31.9–65.0)	22.3 (10.4–41.4)	26.0 (16.1–39.0)
Treatment				
No medications	229	33.4 (22.3–46.8)	14.9 (9.3–22.9)	18.6 (10.7–30.2)
Oral only	426	32.0 (25.2–39.6)	13.8 (9.9–19.0)	18.2 (12.5–25.6)
Insulin only	262	38.1 (28.6–48.6)	18.2 (11.8–27.1)	19.9 (14.2–27.2)
Oral and insulin	45	23.6 (11.4–42.4)	20.1 (8.9–39.3)	3.5 (1.0–11.0)

Gallstone disease is defined as ultrasound-documented gallstones or evidence of a cholecystectomy. All gallstone disease is defined as either of these conditions. Data are standardized to the National Health Interview Survey 1991 diabetic population age 20–74 years using age categories 20–44, 45–64, and 65–74 years.

SOURCE: National Health and Nutrition Examination Survey III 1988–1994

Among non-U.S. studies, in a Chilean Hispanic population at high risk for gallstone disease, persons with insulin resistance

TABLE 26.15. Prevalence and Relative Risk of Ultrasound-Diagnosed Gallstone Disease, by Insulin Resistance Status

POPULATION, YEARS (REF.)	INSULIN RESISTANCE STATUS	SAMPLE SIZE	GALLSTONE DISEASE (%)	ADJUSTED OR (95% CI)
Studies of gallstone disease prevalence				
Participants without diagnosed diabetes, NHANES III, 1988–1994 (97)	Fasting serum insulin (pmol/L)			
	Men	2,672		
	≥80		13.4	0.91 (0.46–1.77)
	58–<80		7.7	0.67 (0.32–1.41)
	46–<58		5.6	0.67 (0.38–1.16)
	35–<46		7.1	0.93 (0.56–1.54)
	<35		5.0	1.0
	Women	2,981		
	≥77		27.4	1.63 (1.11–2.40)
	56–<77		19.5	1.50 (1.07–2.10)
	44–<56		14.7	1.30 (0.89–1.88)
	34–<44		11.1	1.09 (0.74–1.62)
	<34		7.6	1.0
Chilean adults, 2000 (116)	HOMA-IR	881		
	Gallstones			
	4th quartile			1.8 (1.1–3.2)
	1st–3rd quartiles			1.0
	Cholecystectomy			
	4th quartile			2.1 (1.2–3.8)
	1st–3rd quartiles			1.0
	Metabolic syndrome			
	Present			1.7 (1.2–2.5)
	Absent			1.0
Nondiabetic Korean male workers, 2005 (117)	Men	19,503		
	Gallstones			
	HOMA-IR			1.14 (1.04–1.25)
	Metabolic syndrome			
	Present		2.9	1.26 (0.96–1.65)
	Absent			1.0
Study of gallstone disease incidence				
Nondiabetic Italians age 30–69 years, 1985–1993 (118)	Highest insulin quintile	101 cases, 303 controls		2.64 (1.04–6.72)

Conversions for insulin values are provided in *Diabetes in America Appendix 1 Conversions*. CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

SOURCE: References are listed within the table.

in the highest quartile had an 80% higher prevalence of gallstones and over twice the prevalence of cholecystectomy (116). In a large study of nondiabetic Korean men, gallstones on ultrasound were associated with insulin resistance, and this relationship was found regardless of obesity status (117). Persons who met the criteria for the metabolic syndrome had an increased prevalence of gallstone disease in the Chilean study, while there was no statistically significant relationship of the metabolic syndrome with gallstones among Korean men. In the one prospective study of gallstone disease and insulin resistance of which the authors are aware, an increased risk of gallstone disease was found with insulin resistance among those without diabetes. In this Italian nested case-control study, an insulin level in the highest quintile was associated with incident gallstone disease with an odds ratio of 2.64 (118).

In conclusion, among published population-based studies utilizing gallbladder ultrasonography, there has been a fairly consistent association of gallstone disease with diabetes independent of adiposity and other factors. The increased risk has ranged from approximately 40% higher to double among persons with diabetes. The relationship has been more consistent among women than men. This may result from decreased statistical power to detect such a relationship in men, who have a lower prevalence of gallstones. In addition, although the majority of gallstones in the United States are cholesterol stones (119), the proportion of cholesterol stones is lower in men than in women (120,121). An exception with regard to gender difference was a stronger relationship among men in one of the Italian studies of incident gallstone disease (110). In analyses for *Diabetes in America*, age-standardized analyses of the U.S. population discussed above, a similar pattern of increasing gallstone disease prevalence with greater impairment of glucose metabolism was observed among men and women; young, middle-aged, and older adults; and non-Hispanic whites, non-Hispanic blacks, and Mexican Americans.

With regard to the direction of the relationship, it has generally been considered that diabetes predisposes to gallstone disease, though the majority of studies have been cross-sectional. In contrast, a European prospective study found that self-reported gallstone disease preceded the diagnosis of type 2 diabetes (122). An association of insulin resistance with gallstone disease has been shown among those without overt diabetes (117,118). Insulin resistance may be the link between diabetes and gallstone disease.

LIST OF ABBREVIATIONS

A1c. . . . . .glycosylated hemoglobin
ALT. . . . . .alanine aminotransferase
AST . . . . . .aspartate aminotransferase
AUROC . . . . . .area under the receiver operating characteristic curve
BMI . . . . . .body mass index
CI. . . . . .confidence interval
GGT . . . . . .gamma glutamyltransferase
HBcAb . . . . . .hepatitis B core antibody
HBsAg . . . . . .hepatitis B surface antigen
HBV . . . . . .hepatitis B virus
HCC. . . . . .hepatocellular carcinoma
HCV . . . . . .hepatitis C virus
HOMA-IR . . . . .homeostasis model assessment of insulin resistance
HR . . . . . .hazard ratio
MELD. . . . . .Model for End-Stage Liver Disease
MR. . . . . .magnetic resonance
NAFLD . . . . . .nonalcoholic fatty liver disease
NASH. . . . . .nonalcoholic steatohepatitis
NHANES . . . . .National Health and Nutrition Examination Survey
OGTT . . . . . .oral glucose tolerance test
OR . . . . . .odds ratio
RNA . . . . . .ribonucleic acid
SAF . . . . . .standard analysis file
SMR. . . . . .standardized mortality ratio
SRTR . . . . . .Scientific Registry of Transplant Recipients

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.*

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DUALITY OF INTEREST

Drs. Ruhl, Clark, and Everhart reported no conflicts of interest.

REFERENCES

1. Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njolstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J; Emerging Risk Factors Collaboration: Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 364:829–841, 2011
2. Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM: Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. *Diabetes Care* 35:1835–1844, 2012
3. National Health and Nutrition Examination Survey (NHANES) [article online], 2016. Available from *http://www.cdc.gov/nchs/nhanes.htm*. Accessed 3 August 2015
4. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM: Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology* 54:1082–1090, 2011
5. About SRTR Standard Analysis Files (SAFs) [article online]. Available from *https://www.srtr.org/requesting-srtr-data/about-srtr-standard-analysis-files*. Accessed 2 March 2017
6. Rahman R, Hammoud GM, Almashhrawi AA, Ahmed KT, Ibdah JA: Primary hepatocellular carcinoma and metabolic syndrome: an update. *World J Gastrointest Oncol* 5:186–194, 2013
7. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ; American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association: The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Am J Gastroenterol* 107:811–826, 2012
8. National Center for Health Statistics: *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–94. Series 1: Programs and Collection Procedures, No. 32*. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1994
9. Cobbold JF, Patel D, Taylor-Robinson SD: Assessment of inflammation and fibrosis in non-alcoholic fatty liver disease by imaging-based techniques. *J Gastroenterol Hepatol* 27:1281–1292, 2012
10. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, Tiribelli C: The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 6:33, 2006
11. Zelber-Sagi S, Webb M, Assy N, Blendis L, Yeshua H, Leshno M, Ratziu V, Halpern Z, Oren R, Santo E: Comparison of fatty liver index with noninvasive methods for steatosis detection and quantification. *World J Gastroenterol* 19:57–64, 2013
12. Koehler EM, Schouten JN, Hansen BE, Hofman A, Stricker BH, Janssen HL: External validation of the fatty liver index

for identifying nonalcoholic fatty liver disease in a population-based study. *Clin Gastroenterol Hepatol* 11:1201–1204, 2013
13. Calori G, Lattuada G, Ragogna F, Garancini MP, Crosignani P, Villa M, Bosi E, Ruotolo G, Piemonti L, Perseghin G: Fatty liver index and mortality: the Cremona study in the 15th year of follow-up. *Hepatology* 54:145–152, 2011
14. Vernon G, Baranova A, Younossi ZM: Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 34:274–285, 2011
15. Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, Srishord M: Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol* 9:524–530.e1, 2011
16. Clark JM, Brancati FL, Diehl AM: The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 98:960–967, 2003
17. Lazo M, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, Koteish A, Brancati FL, Clark JM: Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol* 178:38–45, 2013
18. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; NASH CRN: Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 362:1675–1685, 2010
19. Ratziu V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, Podevin P, Lacorte JM, Bernhardt C, Bruckert E, Grimaldi A, Poynard T; LIDO Study Group: Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology* 135:100–110, 2008
20. Mahady SE, Webster AC, Walker S, Sanyal A, George J: The role of thiazolidinediones in non-alcoholic steatohepatitis – a systematic review and meta analysis. *J Hepatol* 55:1383–1390, 2011
21. Koteish A, Mae Diehl A: Animal models of steatohepatitis. *Best Pract Res Clin Gastroenterol* 16:679–690, 2002
22. McCullough AJ: Pathophysiology of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 40(Suppl 1):S17–S29, 2006
23. Schuppan D, Schattenberg JM: Non-alcoholic steatohepatitis: pathogenesis and novel therapeutic approaches. *J Gastroenterol Hepatol* 28(Suppl 1):68–76, 2013
24. Rosso N, Chavez-Tapia NC, Tiribelli C, Bellentani S: Translational approaches: from fatty liver to non-alcoholic steatohepatitis. *World J Gastroenterol* 20:9038–9049, 2014
25. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA: High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes* 51:1889–1895, 2002
26. Wannamethee SG, Shaper AG, Lennon L, Whincup PH: Hepatic enzymes, the metabolic syndrome, and the risk of type 2 diabetes in older men. *Diabetes Care* 28:2913–2918, 2005
27. Nannipieri M, Gonzales C, Baldi S, Posadas R, Williams K, Haffner SM, Stern MP, Ferrannini E; Mexico City diabetes study: Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City diabetes study. *Diabetes Care* 28:1757–1762, 2005
28. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'Agostino RB, Jr., Kempf J, Zinman B, Haffner SM; Insulin Resistance Atherosclerosis Study: Elevations in markers of liver injury and risk of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes* 53:2623–2632, 2004
29. Fraser A, Harris R, Sattar N, Ebrahim S, Davey Smith G, Lawlor DA: Alanine aminotransferase, gamma-glutamyltransferase, and incident diabetes: the British Women's Heart and Health Study and meta-analysis. *Diabetes Care* 32:741–750, 2009
30. Abbasi A, Bakker SJ, Corpeleijn E, van der A DL, Gansevoort RT, Gans RO, Peelen LM, van der Schouw YT, Stolk RP, Navis G, Spijkerman AM, Beulens JW: Liver function tests and risk prediction of incident type 2 diabetes: evaluation in two independent cohorts. *PLoS One* 7:e51496, 2012
31. Sun Q, Cornelis MC, Manson JE, Hu FB: Plasma levels of fetuin-A and hepatic enzymes and risk of type 2 diabetes in women in the U.S. *Diabetes* 62:49–55, 2013
32. Suzuki A, Angulo P, Lymp J, St Sauver J, Muto A, Okada T, Lindor K: Chronological development of elevated aminotransferases in a nonalcoholic population. *Hepatology* 41:64–71, 2005
33. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, Kato T, Okuda J, Ida K: The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 143:722–728, 2005
34. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
35. Neuschwander-Tetri BA, Clark JM, Bass NM, Van Natta ML, Unalp-Arida A, Tonascia J, Zein CO, Brunt EM, Kleiner DE, McCullough AJ, Sanyal AJ, Diehl AM, Lavine JE, Chalasani N, Kowdley KV; NASH Clinical Research Network: Clinical, laboratory and histological associations in adults with nonalcoholic fatty liver disease. *Hepatology* 52:913–924, 2010
36. Ong JP, Elariny H, Collantes R, Younoszai A, Chandhoke V, Reines HD, Goodman Z, Younossi ZM: Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. *Obes Surg* 15:310–315, 2005
37. Bugianesi E, Vanni E, Marchesini G: NASH and the risk of cirrhosis and hepatocellular carcinoma in type 2 diabetes. *Curr Diab Rep* 7:175–180, 2007
38. Ong JP, Pitts A, Younossi ZM: Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol* 49:608–612, 2008
39. Dunn W, Xu R, Wingard DL, Rogers C, Angulo P, Younossi ZM, Schwimmer JB: Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. *Am J Gastroenterol* 103:2263–2271, 2008
40. Ruhl CE, Everhart JE: Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. *Gastroenterology* 136:477–485.e11, 2009
41. Lazo M, Hernaez R, Bonekamp S, Kamel IR, Brancati FL, Guallar E, Clark JM: Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study. *BMJ* 343:d6891, 2011
42. Targher G, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, Arcaro G: Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care* 30:2119–2121, 2007

43. de Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, Muggeo M: Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. *Diabetes Care* 22:756–761, 1999
44. Moss SE, Klein R, Klein BE: Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 81:1158–1162, 1991
45. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P: The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 129:113–121, 2005
46. Kim WR, Brown RS, Jr., Terrault NA, El-Serag H: Burden of liver disease in the United States: summary of a workshop. *Hepatology* 36:227–242, 2002
47. Kim WR: The burden of hepatitis C in the United States. *Hepatology* 36(5 Suppl 1): S30–S34, 2002
48. Kim WR, Terrault NA, Pedersen RA, Therneau TM, Edwards E, Hindman AA, Brosgart CL: Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. *Gastroenterology* 137:1680–1686, 2009
49. White DL, Ratziu V, El-Serag HB: Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol* 49:831–844, 2008
50. Everhart J: A confluence of epidemics: does hepatitis C cause type 2 diabetes? *Hepatology* 33:762–763, 2001
51. Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL: Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 133:592–599, 2000
52. Mehta SH, Brancati FL, Strathdee SA, Pankow JS, Netski D, Coresh J, Szklo M, Thomas DL: Hepatitis C virus infection and incident type 2 diabetes. *Hepatology* 38:50–56, 2003
53. Wang CS, Wang ST, Yao WJ, Chang TT, Chou P: Hepatitis C virus infection and the development of type 2 diabetes in a community-based longitudinal study. *Am J Epidemiol* 166:196–203, 2007
54. Montenegro L, De Michina A, Misciagna G, Guerra V, Di Leo A: Virus C hepatitis and type 2 diabetes: a cohort study in southern Italy. *Am J Gastroenterol* 108:1108–1111, 2013
55. Ruhl CE, Menke A, Cowie CC, Everhart JE: Relationship of hepatitis C virus infection with diabetes in the U.S. population. *Hepatology* 60:1139–1149, 2014
56. Yoneda M, Saito S, Ikeda T, Fujita K, Mawatari H, Kirikoshi H, Inamori M, Nozaki Y, Akiyama T, Takahashi H, Abe Y, Kubota K, Iwasaki T, Terauchi Y, Togo S, Nakajima A: Hepatitis C virus directly associates with insulin resistance independent of the visceral fat area in nonobese and nondiabetic patients. *J Viral Hepat* 14:600–607, 2007
57. Stepanova M, Lam B, Younossi Y, Srishord MK, Younossi ZM: Association of hepatitis C with insulin resistance and type 2 diabetes in US general population: the impact of the epidemic of obesity. *J Viral Hepat* 19:341–345, 2012
58. Miyajima I, Kawaguchi T, Fukami A, Nagao Y, Adachi H, Sasaki S, Imaizumi T, Sata M: Chronic HCV infection was associated with severe insulin resistance and mild atherosclerosis: a population-based study in an HCV hyperendemic area. *J Gastroenterol* 48:93–100, 2013
59. Eslam M, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, Romero-Gomez M: Use of HOMA-IR in hepatitis C. *J Viral Hepat* 18:675–684, 2011
60. Conjeevaram HS, Wahed AS, Afdhal N, Howell CD, Everhart JE, Hoofnagle JH; Virahep-C Study Group: Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. *Gastroenterology* 140:469–477, 2011
61. Kawaguchi T, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, Nagao Y, Yanagimoto C, Hanada S, Koga H, Sata M: Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *Am J Gastroenterol* 102:570–576, 2007
62. Kawaguchi Y, Mizuta T, Oza N, Takahashi H, Ario K, Yoshimura T, Eguchi Y, Ozaki I, Hisatomi A, Fujimoto K: Eradication of hepatitis C virus by interferon improves whole-body insulin resistance and hyperinsulinaemia in patients with chronic hepatitis C. *Liver Int* 29:871–877, 2009
63. Romero-Gomez M, Del Mar Viloria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, Corpas R, Cruz M, Grande L, Vazquez L, Munoz-De-Rueda P, Lopez-Serrano P, Gila A, Gutierrez ML, Perez C, Ruiz-Extremera A, Suarez E, Castillo J: Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 128:636–641, 2005
64. Lam KD, Bacchetti P, Abbasi F, Ayala CE, Loeb SM, Shah V, Wen MJ, Reaven GM, Maher JJ, Khalili M: Comparison of surrogate and direct measurement of insulin resistance in chronic hepatitis C virus infection: impact of obesity and ethnicity. *Hepatology* 52:38–46, 2010
65. Brandman D, Bacchetti P, Ayala CE, Maher JJ, Khalili M: Impact of insulin resistance on HCV treatment response and impact of HCV treatment on insulin sensitivity using direct measurements of insulin action. *Diabetes Care* 35:1090–1094, 2012
66. Arase Y, Suzuki F, Suzuki Y, Akuta N, Kobayashi M, Kawamura Y, Yatsuji H, Sezaki H, Hosaka T, Hirakawa M, Ikeda K, Kumada H: Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. *Hepatology* 49:739–744, 2009
67. Simo R, Lecube A, Genesca J, Esteban JI, Hernandez C: Sustained virological response correlates with reduction in the incidence of glucose abnormalities in patients with chronic hepatitis C virus infection. *Diabetes Care* 29:2462–2466, 2006
68. Maeno T, Okumura A, Ishikawa T, Kato K, Sakakibara F, Sato K, Ayada M, Hotta N, Tagaya T, Fukuzawa Y, Kakumu S: Mechanisms of increased insulin resistance in non-cirrhotic patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol* 18:1358–1363, 2003
69. Papatheodoridis GV, Chrysanthos N, Savvas S, Sevastianos V, Kafiri G, Petraki K, Manesis EK: Diabetes mellitus in chronic hepatitis B and C: prevalence and potential association with the extent of liver fibrosis. *J Viral Hepat* 13:303–310, 2006
70. Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, Guo L, Jacob S, Regenstein FG, Zimmerman R, Everhart JE, Wasserfall C, Maclaren NK, Perrillo RP: Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 29:328–333, 1999
71. Imazeki F, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H: Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients. *Liver Int* 28:355–362, 2008
72. Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik J, O'Rahilly S, Shore S, Tom BD, Alexander GJ: Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 30:1059–1063, 1999
73. Bloodworth JM, Jr.: Diabetes mellitus and cirrhosis of the liver. *Arch Intern Med* 108:695–701, 1961

74. Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH: Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol* 17:677–681, 2002
75. Braganca AC, Alvares-da-Silva MR: Prevalence of diabetes mellitus and impaired glucose tolerance in patients with decompensated cirrhosis being evaluated for liver transplantation: the utility of oral glucose tolerance test. *Arq Gastroenterol* 47:22–27, 2010
76. Garcia-Compean D, Jaquez-Quintana JO, Lavalle-Gonzalez FJ, Reyes-Cabello E, Gonzalez-Gonzalez JA, Munoz-Espinosa LE, Vazquez-Elizondo G, Villarreal-Perez JZ, Maldonado-Garza HJ: The prevalence and clinical characteristics of glucose metabolism disorders in patients with liver cirrhosis. A prospective study. *Ann Hepatol* 11:240–248, 2012
77. Muller MJ, Pirlich M, Balks HJ, Selberg O: Glucose intolerance in liver cirrhosis: role of hepatic and non-hepatic influences. *Eur J Clin Chem Clin Biochem* 32:749–758, 1994
78. Tietge UJ, Selberg O, Kreter A, Bahr MJ, Pirlich M, Burchert W, Muller MJ, Manns MP, Boker KH: Alterations in glucose metabolism associated with liver cirrhosis persist in the clinically stable long-term course after liver transplantation. *Liver Transpl* 10:1030–1040, 2004
79. Gundling F, Schepp W, Schumm-Draeger PM: Hepatogenous diabetes in cirrhosis: academic sport or a neglected disease? *Exp Clin Endocrinol Diabetes* 120:469–471, 2012
80. Gentile S, Loguercio C, Marmo R, Carbone L, Del Vecchio Blanco C: Incidence of altered glucose tolerance in liver cirrhosis. *Diabetes Res Clin Pract* 22:37–44, 1993
81. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Haruna Y, Imano E, Suzuki M, Kanda T, Kawano S, Hiramatsu N, Hayashi N, Hori M: Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. *Am J Gastroenterol* 101:70–75, 2006
82. Chen T, Jia H, Li J, Chen X, Zhou H, Tian H: New onset diabetes mellitus after liver transplantation and hepatitis C virus infection: meta-analysis of clinical studies. *Transpl Int* 22:408–415, 2009
83. Kuo HT, Sampaio MS, Ye X, Reddy P, Martin P, Bunnapradist S: Risk factors for new-onset diabetes mellitus in adult liver transplant recipients, an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing database. *Transplantation* 89:1134–1140, 2010
84. Delgado-Borrego A, Liu YS, Jordan SH, Agrawal S, Zhang H, Christofi M, Casson D, Cosimi AB, Chung RT: Prospective study of liver transplant recipients with HCV infection: evidence for a causal relationship between HCV and insulin resistance. *Liver Transpl* 14:193–201, 2008
85. Delgado-Borrego A, Casson D, Schoenfeld D, Somsouk M, Terella A, Jordan SH, Bhan A, Baid S, Cosimi AB, Pascual M, Chung RT: Hepatitis C virus is independently associated with increased insulin resistance after liver transplantation. *Transplantation* 77:703–710, 2004
86. Parolin MB, Zaina FE, Araujo MV, Kupka E, Coelho JC: Prevalence of new-onset diabetes mellitus in Brazilian liver transplant recipients: association with HCV infection. *Transplant Proc* 36:2776–2777, 2004
87. Moon JI, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG: Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: long-term follow up. *Transplantation* 82:1625–1628, 2006
88. Saliba F, Lakehal M, Pageaux GP, Roche B, Vanlemmens C, Duvoux C, Dumortier J, Salame E, Calmus Y, Maugendre D; Diapason Study Group: Risk factors for new-onset diabetes mellitus following liver transplantation and impact of hepatitis C infection: an observational multicenter study. *Liver Transpl* 13:136–144, 2007
89. Schmilovitz-Weiss H, Mor E, Sulkes J, Bar-Nathan N, Shaharabani E, Melzer E, Tur-Kaspa R, Ben-Ari Z: Association of post-liver transplantation diabetes mellitus with hepatitis C virus infection. *Transplant Proc* 35:667–668, 2003
90. Khalili M, Lim JW, Bass N, Ascher NL, Roberts JP, Terrault NA: New onset diabetes mellitus after liver transplantation: the critical role of hepatitis C infection. *Liver Transpl* 10:349–355, 2004
91. Kishi Y, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Makuuchi M: New-onset diabetes mellitus after living donor liver transplantation: possible association with hepatitis C. *Transplant Proc* 38:2989–2992, 2006
92. Baid S, Cosimi AB, Farrell ML, Schoenfeld DA, Feng S, Chung RT, Tolkoff-Rubin N, Pascual M: Posttransplant diabetes mellitus in liver transplant recipients: risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. *Transplantation* 72:1066–1072, 2001
93. Bigam DL, Pennington JJ, Carpentier A, Wanless IR, Hemming AW, Croxford R, Greig PD, Lilly LB, Heathcote JE, Levy GA, Cattral MS: Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. *Hepatology* 32:87–90, 2000
94. Perseghin G, Mazzaferro V, Sereni LP, Regalia E, Benedini S, Bazzigaluppi E, Pulvirenti A, Leao AA, Calori G, Romito R, Baratti D, Luzi L: Contribution of reduced insulin sensitivity and secretion to the pathogenesis of hepatogenous diabetes: effect of liver transplantation. *Hepatology* 31:694–703, 2000
95. Everhart JE, Khare M, Hill M, Maurer KR: Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology* 117:632–639, 1999
96. Everhart JE: Digestive Diseases and Diabetes. In *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 95-1468, 1995, p. 457–483
97. Ruhl CE, Everhart JE: Association of diabetes, serum insulin, and C-peptide with gallbladder disease. *Hepatology* 31:299–303, 2000
98. Hanis CL, Hewett-Emmett D, Kubrusly LF, Maklad MN, Douglas TC, Mueller WH, Barton SA, Yoshimaru H, Kubrusly DB, Gonzalez R, Schull WJ: An ultrasound survey of gallbladder disease among Mexican Americans in Starr County, Texas: frequencies and risk factors. *Ethn Dis* 3:32–43, 1993
99. Everhart JE, Yeh F, Lee ET, Hill MC, Fabsitz R, Howard BV, Welty TK: Prevalence of gallbladder disease in American Indian populations: findings from the Strong Heart Study. *Hepatology* 35:1507–1512, 2002
100. Sampliner RE, Bennett PH, Comess LJ, Rose FA, Burch TA: Gallbladder disease in Pima Indians. Demonstration of high prevalence and early onset by cholecystography. *N Engl J Med* 283:1358–1364, 1970
101. Attili AF, Capocaccia R, Carulli N, Festi D, Roda E, Barbara L, Capocaccia L, Menotti A, Okolicsanyi L, Ricci G, Lalloni L, Mariotti S, Sama C, Scafato E: Factors associated with gallstone disease in the MICOL experience. Multicenter Italian Study on Epidemiology of Cholelithiasis. *Hepatology* 26:809–818, 1997
102. De Santis A, Attili AF, Ginanni Corradini S, Scafato E, Cantagalli A, De Luca C, Pinto G, Lisi D, Capocaccia L: Gallstones and diabetes: a case-control study in a free-living population sample. *Hepatology* 25:787–790, 1997
103. Kono S, Shinchi K, Ikeda N, Yanai F, Imanishi K: Prevalence of gallstone disease in relation to smoking, alcohol use, obesity, and glucose tolerance: a study of self-defense officials in Japan. *Am J Epidemiol* 136:787–794, 1992

104. Kono S, Shinchi K, Todoroki I, Honjo S, Sakurai Y, Wakabayashi K, Imanishi K, Nishikawa H, Ogawa S, Katsurada M: Gallstone disease among Japanese men in relation to obesity, glucose intolerance, exercise, alcohol use, and smoking. *Scand J Gastroenterol* 30:372–376, 1995
105. Sasazuki S, Kono S, Todoroki I, Honjo S, Sakurai Y, Wakabayashi K, Nishiwaki M, Hamada H, Nishikawa H, Koga H, Ogawa S, Nakagawa K: Impaired glucose tolerance, diabetes mellitus, and gallstone disease: an extended study of male self-defense officials in Japan. *Eur J Epidemiol* 15:245–251, 1999
106. Chen CH, Huang MH, Yang JC, Nien CK, Etheredge GD, Yang CC, Yeh YH, Wu HS, Chou DA, Yueh SK: Prevalence and risk factors of gallstone disease in an adult population of Taiwan: an epidemiological survey. *J Gastroenterol Hepatol* 21:1737–1743, 2006
107. Liu CM, Tung TH, Chou P, Chen VT, Hsu CT, Chien WS, Lin YT, Lu HF, Shih HC, Liu JH: Clinical correlation of gallstone disease in a Chinese population in Taiwan: experience at Cheng Hsin General Hospital. *World J Gastroenterol* 12:1281–1286, 2006
108. Lu SN, Chang WY, Wang LY, Hsieh MY, Chuang WL, Chen SC, Su WP, Tai TY, Wu MM, Chen CJ: Risk factors for gallstones among Chinese in Taiwan. A community sonographic survey. *J Clin Gastroenterol* 12:542–546, 1990
109. Misciagna G, Leoci C, Guerra V, Chiloiro M, Elba S, Petruzzi J, Mossa A, Noviello MR, Coviello A, Minutolo MC, Mangini V, Messa C, Cavallini A, De Michele G, Giorgio I: Epidemiology of cholelithiasis in southern Italy. Part II: Risk factors. *Eur J Gastroenterol Hepatol* 8:585–593, 1996
110. Festi D, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, Pazzi P, Mazzella G, Sama C, Roda E, Colecchia A: Incidence of gallstone disease in Italy: results from a multicenter, population-based Italian study (the MICOL project). *World J Gastroenterol* 14:5282–5289, 2008
111. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106:3143–3421, 2002
112. Diehl AK: Cholelithiasis and the insulin resistance syndrome. *Hepatology* 31:528–530, 2000
113. Grundy SM: Cholesterol gallstones: a fellow traveler with metabolic syndrome? *Am J Clin Nutr* 80:1–2, 2004
114. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
115. Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, Fagot-Campagna A, Pettitt DJ, Bennett PH, Knowler WC: Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. *Am J Epidemiol* 151:190–198, 2000
116. Nervi F, Miquel JF, Alvarez M, Ferreccio C, Garcia-Zattera MJ, Gonzalez R, Perez-Ayuso RM, Rigotti A, Villarroel L: Gallbladder disease is associated with insulin resistance in a high risk Hispanic population. *J Hepatol* 45:299–305, 2006
117. Chang Y, Sung E, Ryu S, Park YW, Jang YM, Park M: Insulin resistance is associated with gallstones even in non-obese, non-diabetic Korean men. *J Korean Med Sci* 23:644–650, 2008
118. Misciagna G, Guerra V, Di Leo A, Correale M, Trevisan M: Insulin and gall stones: a population case control study in southern Italy. *Gut* 47:144–147, 2000
119. Diehl AK, Schwesinger WH, Holleman DR, Jr., Chapman JB, Kurtin WE: Gallstone characteristics in Mexican Americans and non-Hispanic whites. *Dig Dis Sci* 39:2223–2228, 1994
120. Trotman BW, Soloway RD: Pigment vs cholesterol cholelithiasis: clinical and epidemiological aspects. *Am J Dig Dis* 20:735–740, 1975
121. Diehl AK, Schwesinger WH, Holleman DR, Jr., Chapman JB, Kurtin WE: Clinical correlates of gallstone composition: distinguishing pigment from cholesterol stones. *Am J Gastroenterol* 90:967–972, 1995
122. Weikert C, Weikert S, Schulze MB, Pischon T, Fritsche A, Bergmann MM, Willich SN, Boeing H: Presence of gallstones or kidney stones and risk of type 2 diabetes. *Am J Epidemiol* 171:447–454, 2010