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REVIEW ARTICLE

DIABETES MELLITUS AND HEPATOBILIARY DISEASE

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SUMMARY

The definition of diabetes mellitus and the various subtypes of the syndrome are identified. Diagnostic criteria are discussed. The hepatobiliary diseases associated with diabetes mellitus and vice versa are discussed with particular attention being given to the mechanisms responsible for the coexistence of the two conditions.

RESUMO

Diabetes mellitus e doença hepatobiliar

Neste artigo define-se diabetes mellitus e caracteriza-se cada um dos seus diversos subtipos discutindo os critérios de diagnóstico. São focadas as diversas patologias hepatobiliares associadas à diabetes mellitus, ou vice versa, com particular enfase nos mecanismos implicados na coexistência destas duas entidades.

Diabetes mellitus is a common metabolic disorder characterized by hyperglycemia in the post-prandial and/or the fasting state which, in its most florid form, is accompanied by ketosis and protein wasting. As such, diabetes mellitus is a syndrome rather than a specific disease entity. Moreover, it is a syndrome which is heterogeneous with respect to its etiology and/or its pathogenesis.

I. DEFINITIONS OF DIABETES MELLITUS AND GLUCOSE INTOLERANCE

With the above listed concepts in mind, the National Institutes of Health, in July 1979, formulated a new classification of diabetes mellitus [1] to include the following five major classes: 1) spontaneous insulin dependent diabetes mellitus; 2) spontaneous insulin independent diabetes mellitus; 3) secondary diabetes mellitus; 4) impaired glucose tolerance; and 5) gestational diabetes mellitus (Table 1).

Annually within the United States, approximately 200,000 new cases of diabetes mellitus are recognized. Thus it is a major health problem with which to be reckoned. Primary or spontaneous diabetes mellitus accounts for over 90% of all cases and is characterized by a progressive increase in vascular and neuropathic complications as the duration of the disease increases. Spontaneous diabetes mellitus is divided into two types termed respectively Type I (formerly called juvenile onset diabetes) and Type II (formerly called maturity onset diabetes) (Table 2). Type II diabetes mellitus accounts for the great majority of cases having a prevalence which is 5 to 10 times that of Type I. In contrast, secondary diabetes mellitus accounts for between 5 to 10% of all cases and its association with long term complications, if any, is difficult to establish. As might be expected, secondary diabetes mellitus like primary diabetes mellitus, is a metabolic syndrome occurring in individuals who have a variety of different predisposing factors or conditions which lead to hyperglycemia (Table 1) rather than a specific disease entity.

TABLE 1 **Classification of Diabetes Mellitus**

1. Spontaneous diabetes mellitus
   - *a*) Type I or insulin-dependent diabetes (formerly called juvenile-onset diabetes)
   - *b*) Type II or insulin-independent diabetes (formerly called maturity-onset diabetes)
2. Secondary diabetes
   - *a*) Pancreatic disease (pancreoprivic diabetes, e.g., panpancreatectomy, pancreatic insufficiency, hemochromatosis)
   - *b*) Hormonal: excess secretion of contrainsulin hormones (e.g., acromegaly, Cushing's syndrome, pheochromocytoma)
   - *c*) Drug induced (e.g., potassium-losing diuretics, contrainsulin hormones, psychoactive agents, diphenylhydantoin)
   - *d*) Associated with complex genetic syndromes (e.g., ataxia telangiectasia, Laurence-Moon-Biedl syndrome, myotonic dystrophy, Friedrich's ataxia
3. Impaired glucose tolerance (formerly called chemical diabetes, asymptomatic diabetes, latent diabetes, and subclinical diabetes): normal fasting plasma glucose, and 2-h value on glucose tolerance test > 140 mg/dl but < 200 mg/dl
4. Gestational diabetes: glucose intolerance which has its onset in pregnancy

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TABLE 2 **Clinical, genetic, and immunologic characteristics of Insulin-dependent (Type I) and Insulin-independent (Type II) diabetes mellitus**

	Insulin-Dependent Diabetes	Insulin-Independent Diabetes
Synonyms	Type I, juvenile-onset diabetes	Type II, maturity-onset diabetes
Age of onset	Usually < 30	Usually > 40
Ketosis	Common	Rare
Body weight	Nonobese	Obese (80 %)
Prevalence	0.5 %	2-4 %
Genetics	HLA-associated (B8, Bw15, Dw3, Dw4) 40-50 % concordance rate in twins	Non-HLA-associated, 95-100 % concordance rate in twins
Circulating islet cell antibodies	50-85 %	< 10 %
Treatment with insulin	Necessary	Usually not required
Complications	Frequent	Frequent

Those individuals who have an abnormality of carbohydrate homeostasis which is demonstrable only on the basis of glucose tolerance testing and in whom the maximum elevation of the plasma glucose level is less than 200 mg/dl but greater than 140 mg/dl are classified as having glucose intolerance rather than overt diabetes mellitus. This distinction from primary diabetes mellitus is made because such patients rarely develop (<1–5 %/year) microangiopathic or neuropathic complications characteristic of primary diabetes mellitus. Moreover, the vast majority are older and reduced glucose tolerance is known to occur with advancing years.

Finally, those individuals who develop glucose intolerance during pregnancy are referred to as having gestational diabetes mellitus.

II DIAGNOSTIC CRITERIA

The diagnostic criteria for the establishment of diabetes mellitus with oral glucose tolerance testing have undergone considerable change recently as a result of the recognition that: 1) any definition is somewhat arbitrary; 2) repeated testing often fails to confirm earlier findings; 3) only a few of the individuals diagnosed as having glucose intolerance on the basis of glucose tolerance testing actually ever go on to develop fasting hyperglycemia; and 4) few if any ever develop microangiopathic or neuropathic changes associated with spontaneous diabetes mellitus. The most recent generally accepted criteria within the United States for the diagnosis of diabetes mellitus based upon glucose tolerance testing are shown in Table 3. However, the results of such tests must always be interpreted with careful consideration of the many factors which are known to diminish performance on formal glucose tolerance testing (Table 4).

III LIVER DISEASE COMPLICATED WITH GLUCOSE INTOLERANCE

Of note is the fact that liver disease per se, and particularly cirrhosis with advanced portosystemic shunting, is associated with glucose intolerance.[2-7] The liver is known to be the principal organ responsible for the catabolism of insulin. Normally 50 % of the insulin secreted by the pancreas is removed by its first passage through the liver. In the presence of cirrhosis, less insulin is extracted by the liver and peripheral circulating insulin levels are increased. Despite such increased plasma levels of insulin, hyperglycemia is common suggesting that peripheral insulin resistance is responsible for the observed glucose intolerance. Consistent

TABLE 3 **Criteria for diagnosis of Diabetes with oral glucose tolerance testing (Plasma glucose concentrations, mg/dl)**

Time (after glucose ingestion), min.	Fajans-Conn	NIH International Workgroup (1979)*	
		Overt Diabetes	Impaired Glucose Tolerance
30			
60	195	1 value > 200	1 value > 200
90	165		
120	140+	> 200	> 140+ and < 200

* National Diabetes Data Group: Diabetes 1979; 29: 1039.

\+ In patients above age 50 this value should be age-adjusted by adding 10 mg/dl for each decade beyond the fifth.

TABLE 4 **Factors diminishing performance on Glucose tolerance testing**

1. Age: ↑ 10/dl per decade beyond the fifth decade
2. Inactivity
3. Diet (if < 100 g carbohydrate per day)
4. Drugs
   - *a*) Potassium-wasting diuretics
   - *b*) Dilantin
   - *c*) Alcohol (large amounts)
   - *d*) Corticosteroids
   - *e*) Oral contraceptives
   - *f*) Psychoactive drugs
5. Intercurrent disease
   - *a*) Endocrine
   - *b*) Renal failure
   - *c*) Cirrhosis
   - *d*) Nonspecific severe stress
     - (1) Myocardial infarction
     - (2) Sepsis

with such a hypothesis, peripheral monocytes obtained from individuals with cirrhosis have been shown to have reduced numbers of insulin receptors.[8, 9] The specific mechanisms responsible for the reduced number of cellular receptors and the resultant insulin resistance however, are not known.

Specific types of liver disease are known to be more commonly associated with glucose intolerance and/or overt diabetes mellitus than are others. Thus hemochromatosis, a metabolic disorder of iron metabolism is almost always associated with identifiable glucose intolerance if not overt diabetes mellitus. The excess iron accumulated in ths disease is deposited preferentially in the liver, pancreatic islets and the myocardium. As a result, hepatic fibrosis, diabetes mellitus and clinical cardiac disease are the three common manifestations of the disease.

Similarly, the autoimmune forms of chronic active liver disease which are often associated with thyroiditis, Sjögren's syndrome, rheumatoid arthritis, and various other putative autoimmune diseases are associated commonly with diabetes mellitus.[10] Moreover, both diabetes mellitus and autoimmune liver disease are characterized by the inheritance of specific HLA alleles.[11] In particular, the relative risk for diabetes mellitus is 3.1 fold increased in individuals who carry the HLA B8 allele. Similarly, the HLA DW3 allele carries a 3.7 fold increased risk for diabetes mellitus. Moreover, both alleles plus the HLA A1 allele are found more commonly (2 fold increased risk) in individuals who have autoimmune chronic active hepatitis than in control populations. Thus, the inheritance of the HLA B8 and DW3 alleles may predispose the individual to both diabetes mellitus and autoimmune chronic active hepatitis.

TABLE 5 **Histopathology of the liver in Diabetes Mellitus**

Glycogen — infiltration of the nucleus	50 % (12-85 %)
Fatty Liver — large droplet type	50 % (30-80 %)
Steatonecrosis — hyaline and fibrosis but no polymorphonuclear leukocytes	Unknown
Cirrhosis — micronodular	16 % (0.4-30 %)

IV DIABETES MELLITUS AND LIVER DISEASE

Even in the absence of recognizable common heritable factors, liver disease and in particular fatty liver is common in individuals with diabetes mellitus (Table 5).[12-28] Thus, large droplet hepatic steatosis has been reported to occur in 30-80 % of diabetics with the mean reported value indicating that about 50 % of diabetic individuals manifest evidence of a fatty liver. Such individuals often have a large tender liver and not uncommonly have elevations of one or more of the standard liver injury tests (transaminases, alkaline phosphatase and glutamyl transpeptidase). Moreover, functional tests of hepatic function such as BSP and ICG clearances as well as serum bilirubin levels are abnormal in approximately 80 % of diabetics with a fatty liver. Even in the absence of a histologic demonstration of fatty liver, glycogen infiltration of the hepatocyte cytoplasm and nucleus is common in diabetic individuals when the liver is examined histologically and has been reported to occur in approximately 50 % of all diabetics (published rates 12--85 %).

V MECHANISMS RESPONSIBLE FOR FATTY LIVER

What are the mechanisms by which fatty liver occurs so frequently in diabetic patients? Fat, particularly triglyceride fat, can accumulate in the liver for any of several reasons. These include: 1) increased uptake from peripheral fat depots; 2) increased hepatic triglyceride synthesis from either carbohydrates or nonesterified fatty acids; 3) reduced hepatic oxidation of fat; 4) reduced hydrolysis by lysosomal lipase; 5) reduced formation of VLDL; 6) reduced hepatic release of newly formed VLDL; and 7) a combination of any two or more of the above abnormalities[29] (Figure 1).

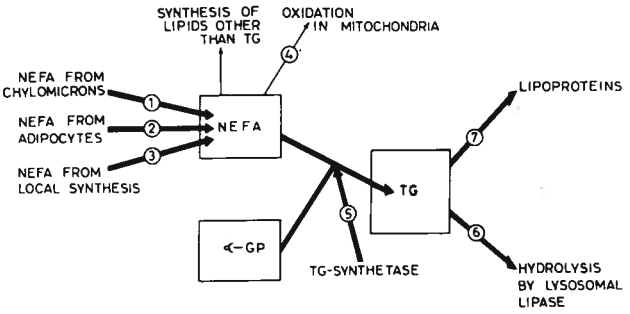

Figure 1 Metabolism of nonesterified fatty acid (NEFA) or free fatty acid (FFA) within the liver. Fatty acids are presented to the liver following ingestion of a meal from 1) chylomicrons, during periods of fasting from 2) peripheral fat stores, and 3) from local hepatic synthesis. Once within the liver, fatty acids are used for triglyceride synthesis, the synthesis of other lipids such as cholesterol, phospholipids and glycolipids, or 4) oxydized in mitochondria. The principal fate of hepatic fatty acid, however, is triglyceride synthesis. Once triglycerides are formed they can be disposed of by hydrolysis in 6) lysosomes by lysosomal lipase (minipathway) or incorporated into 7) lipoproteins, especially VLDL (major pathway).

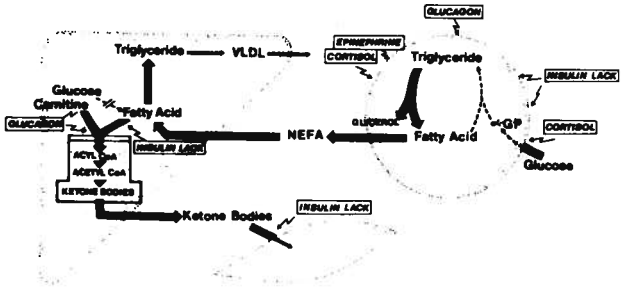

Figure 2 Schematic representation of the effect of various hormones upon lipid metabolism as it relates to the diabetic and the uptake and storage of fat by the liver. Insulin deficiency alone or in combination with epinephrine and cortisol and glucagon excess inhibits glucose uptake by adipocytes and enhances triglyceride lipolysis, thereby increasing plasma levels of NEFA or FFA levels. Free fatty acids are taken up by the liver while insulin deficiency and glucagon excess enhance ketone body formation and triglyceride synthesis.

It is also well established that the rate of hepatocyte uptake of free fatty acids (FFA) from plasma is concentration-dependent.[30-31] Thus as the plasma level of FFA increases so does the rate of hepatic uptake. Moreover, it is well known that either insulin deficiency or glucagon excess (the principal defects in diabetes mellitus) enhance adipocyte lipolysis and inhibit glucose uptake and therefore triglyceride formation by adipocytes (Table 6 and Figure 2). Thus the same factors which enhance the net plasma level of FFA also increase the amount of fat available to the liver for uptake. Moreover, within the liver, insulin deficiency or glucagon excess enhances glycogen degradation and gluconeogenesis while inhibiting glucose utilization[30] (Figure 2). As a result, the requirement for hepatic oxidation of fat is enhanced. Unfortunately, the various mechanisms by which the hepatocyte is able to dispose of fat are limited with the single exception of triglyceride formation. As a result the hepatic content of triglyceride progressively increases and fatty liver results.[29]

Several factor unique to diabetics and obese individuals and particularly to the obese diabetic with Type II diabetes also might contribute to the high prevalence of fatty liver in such individuals. These include an enhanced rate of basal adipocyte lipolysis in obese individuals and a further enhancement of the basal rate of adipocyte lipolysis in diabetics. Moreover, effective starvation as occurs in ketoacidosis, and increases in plasma glucocorticoids which are known to be increased in the plasma of diabetics with ketoacidosis also both enhance adipocyte lipolysis.

Therefore, the principal factors thought to be responsible for the fatty liver in individuals with diabetes mellitus are:

1. increased adipocyte lipolysis
2. increased hepatic uptake of FFA
3. increased hepatic triglyceride synthesis; and
4. limited hepatic disposition of fat except as stored cytoplasmic triglyceride.

VI MORE ADVANCED LIVER DISEASE AND DIABETES MELLITUS (Table 5)

More recently, hepatic steatonecrosis characterized by large droplet fat, hepatic fibrosis and occasionally the presence of hyaline, similar to that which is seen in the liver of alcoholics, has been described in diabetic individuals who have little or no history of alcohol use.[18] This lesion also includes perivenular fibrosis of the terminal hepatic vein, but unlike the lesion of alcoholic hepatitis, is characterized by the absence of polymorphonuclear leucocytes in the hepatic lobule.[18, 24, 27] Unlike simple diabetic hepatic steatosis, steatonecrosis, like alcoholic hepatitis, may be a forerunner of cirrhosis in some diabetic individuals. The evidence for this latter statement however, is meager indeed. It includes only a reported incidence of portal cirrhosis of 16 % in diabetics who come to autopsy. This figure however, is twice the risk for cirrhosis seen in the general autopsy population.

The specific factors that enable the individual diabetic to develop the lesion of steatonecrosis as compared to simple steatosis are entirely unknown. Whether specific HLA alleles are associated with its occurrence has yet to be studied. Moreover, the frequency with which it progresses to cirrhosis is not known but it is expected to be in the range of 75 to 100 % of cases based upon the reported frequency of the two lesions in diabetic populations.

TABLE 6 **Insulin deficiency and/or Glucagon excess**

Carbohydrate Metabolism	**Fat Metabolism**
Decreased uptake	Increased lipolysis
Increased production	Increased ketogenesis
	Increased hepatic triglyceride synthesis
Results	
Hyperglycemia	
Hypertriglyceridemia	

TABLE 7 **Hepatotoxic reactions of oral hypoglycemic agents**

Sulfonylurea agents (0.5 to 1.0 %)	
Intrahepatic cholestasis	
Granulomas	
Acetohexamides	
Hepatocellular necrosis	
Biguanides	
No hepatotoxicity recognized	

TABLE 8 **Postoperative complication rate of cholecystectomy**

Diabetics	60-70 %
Obesity	10-20 %
Controls	5-10 %

VII THERAPY-ASSOCIATED LIVER DISEASE

Not only are diabetics at increased risk to develop hepatocellular disease as a direct consequence of their diabetes per se, but they are also at risk to develop hepatic disease as a consequence of the medical treatment applied for the management of their primary endocrine disease process. Specifically insulin therapy enhances the risk of the individual to acquire any of a variety of parenterally acquired hepatic di-

seases particularly hepatitis B and Non A Non B viral infections. The risk of acquiring these two particular viral diseases, as a consequence of parenteral insulin therapy, is particularly great among insulin dependent adolescent (Type I) diabetics who may share needles and syringes at special recreational camps for such patients.

Adults with insulin independent diabetes mellitus like those with insulin dependent diabetes are also at increased risk to develop liver disease as a consequence of their medical therapy (Table 7). The iatrogenic liver diseases that can occur in such individuals are due principally to the occasional development of either cholestatic or granulomatous liver disease as a result of sulfonylurea therapy.[32, 33] Such idiosyncratic reactions tend to occur early, usually within 4 to 6 weeks of onset of the use of the particular drug in question, and occur most commonly with chlorpropamide, less often with tolbutamide and least often with tolazamide.

In constrast to the occasional occurrence of cholestasis with sulfonylurea drugs, acetohexamide therapy is associated very rarely with the development of hepatocellular injury which although quite rare, may be severe.

VIII. GALLSTONE DISEASE AND DIABETES MELLITUS

In addition to primary hepatocellular disease, diabetics are at increased risk for the development of gallbladder disease and the hazards of cholelithiasis in particular.[34-35] Specifically, diabetics appear to have a 1 to 1.5 fold increased risk of developing cholelithiasis due principally to their increased secretion of bile supersaturated with cholesterol in relation to their secretion of bile acids. This finding of increased biliary lithogenicity is particularly common in adult onset Type II diabetics, who also are commonly obese and female, two factors recognized as contributing to the pathogenesis of cholesterol gallstone disease. Thus it is difficult, if not impossible to sort out the individual effects of obesity, female sex or estrogenity, diabetes mellitus per se and the associated hyperlipoproteinemic states (Type IIA, IIB and IV) which are commonly seen in diabetics, in the pathogenesis of this increased prevalence of gallstones in the adult insulin independent diabetic population.

Both insulin therapy and diabetes mellitus are associated with gallstone disease.[34, 35, 37-45] Thus, patients with insulin dependent diabetes synthesize more cholesterol and bile acid than do normal controls whether studied on or off insulin therapy (Figure 3). Interestingly however, with continued insulin therapy the bile acid synthesis rate declines somewhat although still remaining increased compared to that of normal controls while cholesterol synthesis rate do not change. As a result, the saturation index of hepatic bile which is increased in diabetics not using insulin increases further with insulin therapy (Figure 4).

Moreover, reduced contractibility of the gallbladder and reduced intestinal transit, occurring as a consequence of diabetic visceral neuropathy, may contribute importantly to the pathogenesis of cholesterol cholelithiasis in adult diabetics.[35-37, 40] Such phenomena reduces the frequency of enterohepatic cycling of the bile salt pool and results therefore in an expansion of both the bile salt pool and biliary cholesterol secretion.[32-34] Such responses allow cholesterol to accumulate within the gallbladder, in excess of the other solubilizing biliary lipids. In addition, gallbladder distention and

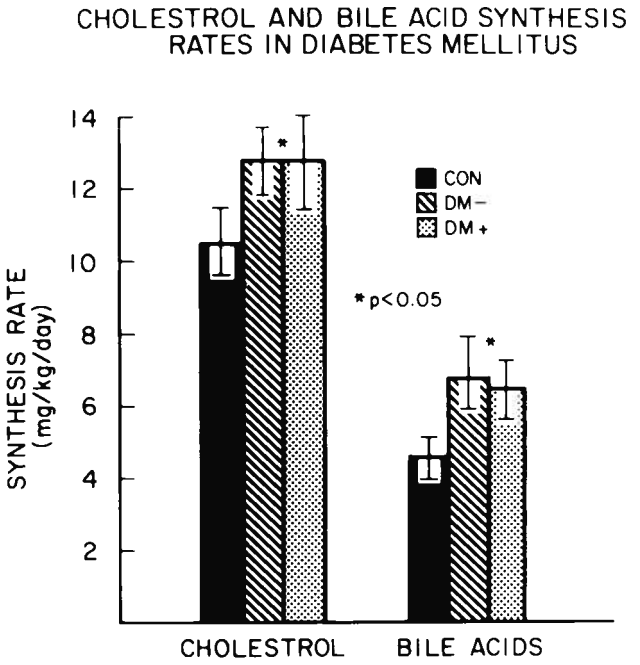

Figure 3 Cholesterol and bile acid synthesis rates in controls (con), diabetics not taking insulin (DM−) and diabetics using insulin (DM+). Bars represent mean values and the brackets represent SEM.

stagnation associated with diabetic neuropathy allows such supersaturated bile to precipitate its cholesterol content and the resultant stones to grow.

Elective surgery for gallstones in diabetics is not particularly dangerous when one corrects for the increased prevalence of postoperative infections that occur in obese patients[43] (Table 8). In contrast, emergency gallbladder sur-

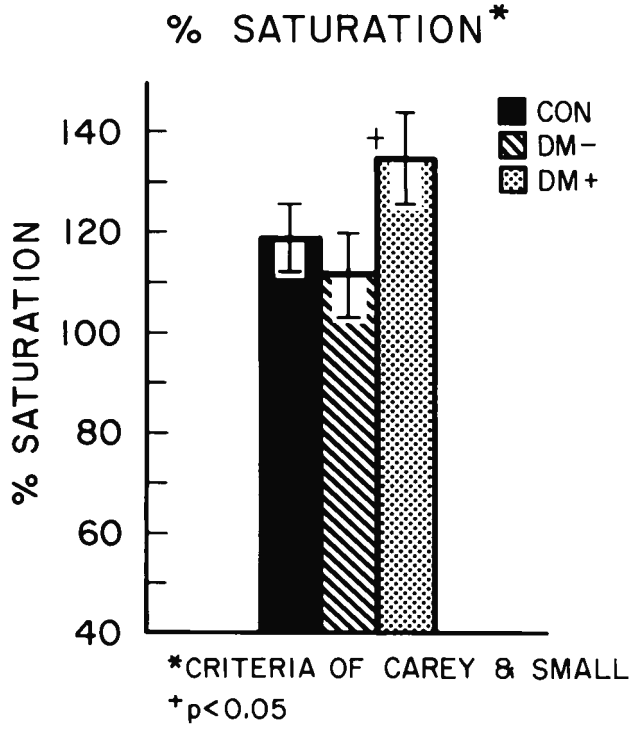

Figure 4 Saturation of hepatic bile with biliary lipids in control nondiabetics (con), diabetics not requiring insulin (DM−), and insulin requiring diabetics (DM+). Bars represent mean values and brackets the SEM.

gery in diabetics is associated with a substantial 15-20 % mortality and 60-70 % risk of postoperative wound infections as compared to a 4-5 % mortality and 5-10 % risk of wound infection in nondiabetic lean patients [41,42] (Table 9). As a result of these statistics, elective gallbladder surgery is recommended frequently for diabetics with gallstones even in the absence of prior biliary tract symptoms.

TABLE 9 **Emergency gallbladder surgery and Diabetes Mellitus**

Diabetics	Mortality rate	15-20 %
Nondiabetics	Mortality rate	4- 5 %

Elective surgery mortality rates do not differ.

As must be obvious from the above discussion, hepatobilliary disease and diabetes mellitus commonly coexist. Thus both the gastroenterologist and the diabetologist are called often to care for patients with one or the other disease or both disease processes. Moreover, the management of each process can be affected adversely by the presence of the other. Therefore, physicians of both specialties must be aware of the management of these two disease processes in the presence of the other and the differences in the approach to either disease which pertain when they occur in the presence of the other.

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