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Hepatic Arteriolosclerosis: A Small Vessel Complication of Diabetes and Hypertension

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Abstract

Background & Aim—Liver involvement in diabetes is well recognized in the form of steatohepatitis and glycogenic hepatopathy. More recently sinusoidal fibrosis, even in the absence of steatosis has also been suggested to be associated with diabetes (diabetic hepatosclerosis) however, case control studies are lacking. In addition, microangiopathy (hyaline arteriolosclerosis), a well-known complication of diabetes, has not been well studied in liver. Therefore, we undertook a cross-sectional blinded study with the specific aim of evaluating the association between hepatic sinusoidal fibrosis and hepatic arteriolosclerosis (HA) with diabetes.

Methods—Liver biopsy findings from 89 diabetic patients obtained between January 2006 and December 2009 were compared to those of 89 non-diabetic patients matched by age and HCV infection status. Patients with cirrhosis, liver mass, right heart failure, significant alcohol use, or insufficient available clinical information were excluded. Medical records were reviewed for the presence of diabetes, BMI, diabetes treatment, and comorbidities at time of biopsy (e.g. underlying liver disease, hypertension, dyslipidemia). Liver biopsies were evaluated blinded to all clinical data (including presence or absence of diabetes) for a variety of histologic features, especially patterns of fibrosis and HA.

Results—Diabetics had a higher average BMI (33m/kg² vs. 30m/kg², p=0.0039), prevalence of hypertension (78% vs. 33%, p <0.0001) and dyslipidemia (52% vs. 20%, p<0.0001). Among diabetics, 87% had type 2 diabetes and 57% used insulin. While sinusoidal fibrosis, with or without steatosis, was not significantly associated with the presence of diabetes, HA was significantly more prevalent among diabetics compared with controls: 45% vs. 29% (p=0.0298). The presence of both diabetes and hypertension had a significant odds of HA: with an adjusted odds ratio of 2.632 (95% CI 1.178–5.878, p=0.0183). Biliary changes were associated with HA in some cases (10.6%).

Conclusions—In this study we describe the histopathological entity of hepatic arteriolosclerosis for the first time. It is a small vessel complication (microangiopathy) of the liver observed in mainly in patients with diabetes who also have arterial hypertension. The clinical and prognostic implications of this finding, particularly regarding liver injury, remain to be further investigated.

Keywords

diabetes; hyaline arteriolosclerosis; hepatic arteriolosclerosis; hepatic microangiopathy; microvascular disease

Introduction

Diabetes is associated with an increased risk of chronic liver disease (1), fibrosis progression in patients with chronic hepatitis C (2, 3), and progression to cirrhosis and its decompensation (4). Diabetes has two well accepted hepatic manifestations. The first is non-alcoholic steatohepatitis (NASH) which is a complication of insulin resistance and is the purported main reason for the higher risk of chronic liver disease among diabetic patients. The second is glycogenic hepatopathy, described more frequently in patients with type 1 diabetes and considered the consequence of hyperglycemia, characterized by glycogen accumulation within the hepatocyte cytoplasm. (5–9)

Outside of the liver, microvascular complications (microangiopathy) are the characteristic long-term consequences of hyperglycemia in diabetic patients. Microvascular complications may involve arterioles and/or capillaries. Arteriolar involvement is characterized by “hyaline arteriolosclerosis” which is marked by the deposition of glycated protein within the arteriolar walls and consequent wall thickening and narrowing of the arteriolar lumen. Capillary involvement is characterized by diffuse capillary basement thickening (10). Organs with limited collaterals and/or end arteries are most affected as a result of microangiopathy leading to tissue injury. Nephropathy, retinopathy and peripheral neuropathy are well-recognized manifestations of diabetic small vessel disease. In addition, involvement of small vessels in other organs such as the heart, muscle, and brain has also been recognized (11–13).

Though diabetic microvascular complications are well described systemically, these are not well-recognized or well characterized in the liver. Previous animal studies and descriptive case studies analyzing liver biopsies of diabetic patients have identified hepatic sinusoidal abnormalities (14–16). These have been described as a dense, diffuse sinusoidal fibrosis in the absence of features of NASH which has been called “diabetic hepatosclerosis.” The largest case series analyzed the liver biopsies of only 12 diabetic patients (17). Diabetic hepatosclerosis has been considered an alteration of the microvasculature representative of a diabetic microangiopathy of the liver.

Subsequent descriptive studies further characterized this finding through retrospective review of liver tissue obtained from autopsies of diabetic patients. These studies identified a prevalence of 2–12% of diabetic hepatosclerosis among diabetics (18, 19). In addition, studies have identified other “nonspecific” findings that included hyaline arteriolosclerosis of the hepatic arterioles (18, 20).

The aim of this study is to assess the presence of histological evidence of microangiopathy of the liver in a cross-sectional study in which liver biopsies of patients with diabetes were compared (in a blinded fashion) to a matched population of non-diabetic controls. We hypothesized that microvascular abnormalities of the liver – represented by a diffuse sinusoidal fibrosis or hepatic hyaline arteriolosclerosis (HA) – would be more prevalent among diabetics compared to non-diabetic controls.

Materials and Methods

Study Design

This study is a cross-sectional comparative study examining the presence of small vessel abnormalities in patients with diabetes vs. matched controls without diabetes.

Consecutive patients who underwent liver biopsy for any indication at Yale New Haven Hospital, New Haven CT between January 2006 and December 2009 were identified through the pathology database accrued prospectively at the Department of Pathology of Yale University. Clinical exclusion criteria were: age <10 years and the presence of documented conditions known to be associated with sinusoidal fibrosis such as: history of right heart failure, heavy alcohol use (>7 drinks/day for women; >14 drinks/day for men; or documented alcohol abuse or dependence in the chart), prolonged TPN use, history of liver transplant or concern for graft-versus-host disease or veno-occlusive disease. Histological exclusions were a histological diagnosis of cirrhosis and biopsy of a liver tumor. In addition, patients were excluded if medical records contained insufficient information.

Variables

Clinical Data—Demographic, clinical, and biochemical data were collected from the electronic medical records. The presence or absence of the following co-morbidities was recorded: dyslipidemia defined by use of statin within 1 year of biopsy or diagnosis of “hyperlipidemia” in the chart, arterial hypertension, coronary artery disease, and peripheral artery disease (these were defined by documentation of this in the medical record prior to the date of biopsy). The presence of HCV infection was defined by a positive anti-HCV antibody and a confirmatory positive HCV-RNA within one year of the biopsy with histological evidence of hepatitis C. The presence of chronic hepatitis B infection was defined by the presence of positive hepatitis B surface antigen, positive core antigen and negative surface antibody with confirmatory viremia within 1 year of biopsy in all patients.

Tobacco and alcohol use were classified as absent in the absence of any tobacco/alcohol use. Otherwise, it was classified as being present (regardless of quantity).

The absence/presence of microvascular complications were reviewed for all diabetes patients when information was available. Documentation of any diabetic retinopathy (non-proliferative or proliferative retinopathy) was recorded as “diabetic retinopathy present.” Documentation of microalbuminuria, chronic renal insufficiency from diabetes, or diabetic end-stage renal disease was recorded as “diabetic nephropathy present.” Documentation of diabetic neuropathy or use of pre-gabapentin or gabapentin for neuropathy was documented as “diabetic neuropathy present.” Documented negative screening for retinopathy,

nephropathy, or neuropathy within 1 year of biopsy was recorded as absence for the microvascular complication.

AST, ALT, alkaline phosphatase, total bilirubin, and hemoglobin A1C were recorded from within 6 months of biopsy.

Histopathology—All liver biopsies were evaluated by the same experienced pathologist (DJ) without knowledge of the clinical and laboratory data and study group (diabetic or non-diabetic). The parameters analyzed are shown in Table 1.

Routine hematoxylin and eosin stain (H & E stain), trichrome, reticulin, iron (Prussian blue stain) and D-PAS (period acid Schiff following diastase digestion) stains were evaluated in all cases. In select cases PAS stain was also performed. Standard evaluation of all liver biopsies for steatosis, steatohepatitis, glycogenated nuclei, pattern of fibrosis, inflammation (portal and lobular) and siderosis was done. In addition, special attention was given to vascular changes, bile ducts and portal tract collagen. Steatosis, steatohepatitis, inflammatory activity score, fibrosis grade and siderosis were graded using commonly used systems (21–23), while other features were graded or scored as shown in table 1.

The main vascular changes evaluated were of the hepatic arterioles and sinusoids. Hepatic arteriolosclerosis was identified as thickening of the arteriolar wall and graded as mild to severe (Figure 1A–D) (Table 1). When hepatic arteriolosclerosis was present, the extent of involvement was quantified based on number of portal tracts involved (<25%, 25–50%, >50% portal tracts involved) and intensity of D-PAS staining in vessels involved by hepatic arteriolosclerosis was subjectively graded from mild to severe (Figure 2A–B). Presence of sinusoidal fibrosis and zone of hepatic lobules involved were also noted. When the portal collagen had a hyaline or smudgy appearance, it was recorded as hyalinization of portal tracts (Figure 1C & D). Presence and absence of any biliary changes in the form of inflammation, duct loss, reactive epithelial changes or ductular reaction (figure 3A–B) were also documented.

Outcomes

This study compares a nondiabetic group and diabetic group on the prevalence of three main outcomes: “diabetic hepatosclerosis” defined as the presence of sinusoidal fibrosis in the absence of steatosis (primary outcome); presence of any sinusoidal fibrosis with or without steatosis (secondary outcome); and/or the presence of hepatic arteriolosclerosis (secondary outcome).

Statistical Analysis

Power analysis—The prevalence of diabetic hepatosclerosis in diabetic patients has been described in two small studies: one showing a prevalence of 2% among 57 diabetics (18) and another one, the largest, showing a prevalence of 12% among 159 diabetics (19). Assuming a 12% prevalence of “diabetic hepatosclerosis” among diabetics and none in non-diabetics and allowing for 5% type I error, a sample size of 89 patients in each group yields 85% power to detect a significant difference.

Age is associated with hyaline arteriolosclerosis (24) and hepatitis C is associated with steatosis. Therefore, the diabetic and nondiabetic groups were frequency matched on age and HCV infection.

Dichotomous variables were expressed as proportions and compared using the chi-square analysis. Non-normally distributed continuous variables were expressed as medians with ranges and compared using Wilcoxon rank sum test. Chi Square analysis was used to determine outcomes with significant association with diabetes. Variables thought likely to be associated with the significant outcomes were assessed by univariate analysis. Multicollinearity between dichotomous predictor variables was examined using Pearson Chi Square analysis. Predictor variables found to have a p-value of less than 0.05 on univariate analysis and not to have multicollinearity were included in a multiple logistic regression model predicting the absence/presence of the outcome.

RESULTS

As shown in Figure 4, 1440 liver biopsies were performed during the time period analyzed with a majority being excluded because of insufficient medical records. A total of 89 liver biopsies from diabetic patients qualified for the study and were matched by age and presence (or absence) of HCV infection to 89 non-diabetic patients. A group of 89 age and hepatitis C matched non-diabetic patients were identified and included.

Population Characteristics

As expected, given the matching performed, nondiabetic and diabetic groups had a similar median age (51y) and HCV infection prevalence (60% v 57%, respectively) (Table 2a).

The proportion of males in the diabetes group (42%) was lower than in the non-diabetic group (56%). Diabetic patients had a significantly higher body mass index and a higher prevalence of hypertension, dyslipidemia, coronary artery disease and peripheral vascular disease. Exposure to alcohol and tobacco smoking was equal between the two groups as was the prevalence of hepatitis B infection. The indications for liver biopsy were similar in both groups with the main indications being staging of hepatitis C. There were no patients with primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) in either group. The median value of alkaline phosphatase was slightly higher in diabetics (93 vs. 84 IU/L).

The majority of the 89 diabetic patients had type 2 diabetes (87%) (table 2b). Median hemoglobin A1C measurement from within 6 months of liver biopsy was 7.6% (4.6%–15.8%). Among those with available information: 53% had at least one documented diabetic microvascular complication; 18% had retinopathy; 41% had neuropathy; and 37% had nephropathy.

Table 2c presents the liver histopathology characteristics of both groups. As expected, both steatosis and steatohepatitis were significantly more prevalent among diabetics compared with nondiabetics (steatosis: 60% v 40% p value=0.01; steatohepatitis: 41% v 25% p value=0.03). Fibrosis stage was not different between groups.

Primary and Secondary Outcomes

Neither “diabetic hepatosclerosis” (sinusoidal fibrosis in the absence of steatosis) nor sinusoidal fibrosis in general were significantly more prevalent among diabetics (table 3). However, hepatic arteriolosclerosis was more prevalent among diabetics compared with nondiabetic controls (29% vs. 45%, $p=0.03$).

Clinical Predictors of Hepatic Hyaline Arteriosclerosis

The clinical characteristics of patients with and without hepatic arteriolosclerosis are shown in Table 4. Those with hepatic arteriolosclerosis were more likely to be female, older, and have diabetes, hypertension, and dyslipidemia than those without hepatic arteriolosclerosis.

Logistic regression was employed to examine the association between diabetes and hepatic arteriolosclerosis. On univariate analysis, age, sex, diabetes, hypertension, dyslipidemia, CAD, and PVD were significantly predictive of hepatic arteriolosclerosis (table 5).

Diabetes was associated with both hypertension and dyslipidemia. Diabetes and arterial hypertension were very strongly correlated as 78% of the included diabetics had concomitant hypertension. In order to investigate the interaction of diabetes and hypertension with hepatic arteriolosclerosis a four level variable was created to represent the following scenarios: absence of hypertension and diabetes ($n=58$); presence of both hypertension and diabetes ($n=68$); presence of hypertension only (28); and presence of diabetes only (19). A multivariate model was built using this four level variable, age, and sex. CAD and PVD were not included in the multivariate model since these parameters are not the cause of microvascular disease but rather the result of the same factors that lead to microvascular complications.

The adjusted OR for the presence of concomitant diabetes and hypertension was significant at 2.551 (95% confidence interval 1.142–5.697, $P=0.0223$). The presence of diabetes alone or hypertension alone did not result in an increased odds of hepatic arteriolosclerosis compared to those with neither diabetes nor hypertension. The adjusted OR of female gender and increasing age for predicting hepatic arteriolosclerosis were significant at 2.015 (95% CI 1.041–3.900, $P=0.0375$) and 1.027 (95% CI 1.001–1.055, $P=0.0424$) respectively.

Among diabetics, a correlation between the presence of hepatic arteriolosclerosis and hemoglobin A1C, presence of other microvascular complications (diabetic retinopathy, nephropathy, neuropathy), or insulin use was not identified.

Distribution of hepatic arteriolosclerosis

The hepatic arteriolar changes seen in hepatic arteriolosclerosis involved >25% of portal tracts in 57 of the 66 cases. There was no significant difference in the distribution of portal tract involvement between diabetics and non-diabetics.

Liver enzymes and histopathology associated with hepatic arteriosclerosis

A statistically significant difference was not seen in median AST, ALT, alkaline phosphatase, and total bilirubin between patients with and without hepatic arteriolosclerosis.

14 patients with hyaline arteriolosclerosis had an abnormally elevated alkaline phosphatase and, of those, 8 were diabetic.

The associations between hepatic arteriolosclerosis and the presence of other histological findings are shown in table 7. Given that the association between hepatic arteriosclerosis and 11 different histological variables are examined, Bonferroni correction for multiple comparisons required considering a p-value <0.0045 as significant. A significant association was found between hepatic arteriolosclerosis and the presence of pericentral fibrosis, sinusoidal fibrosis, and hyalinization of the portal tract. A non-significant trend was found for an association between hepatic arteriolosclerosis and microscopic biliary changes. The biliary changes that were seen most frequently were biliary ductular proliferation (n=13), inflammatory duct injury (n=2), reactive ducts only (n=1), reactive ducts with cholestasis (n=2), and duct loss and cholestasis (n=1) (figure 3A–B).

All cases of hepatic arteriolosclerosis were reviewed to evaluate for differences in absence or presence of PAS positive material in arteriolar wall between diabetics and non-diabetics using both PAS and D-PAS stains. Among the total of 66 cases with hepatic arteriolosclerosis, 40 were diabetic and 26 were non-diabetic. Positive PAS staining was seen in 17 diabetic (43%) and 5 nondiabetic hepatic arteriolosclerosis cases (19%) (p=0.06) and there was no difference between PAS or DPAS stains.

DISCUSSION

Diabetes and insulin resistance are highly prevalent metabolic conditions that negatively impact the outcomes of patients in general and particularly those with underlying liver disease. The main systemic morbidity of diabetes is related to its microvascular complications. We undertook this study to identify microvascular abnormalities of the liver that may be associated with diabetes.

We did not find any significant difference in the presence of the so-called “diabetic hepatosclerosis” –previously postulated to be a form of diabetic microangiopathy in the liver — or the presence of sinusoidal fibrosis (with or without steatosis) between diabetic and nondiabetic patients. This is not entirely surprising as it is well recognized that sinusoidal fibrosis can result from a variety of causes, some of which may not be clinically obvious at a given time and its presence is not necessarily indicative of diabetes.

Our aim was also to assess the association of diabetes with hyaline arteriolosclerosis in the liver (hepatic arteriolosclerosis). We found that hepatic arteriolosclerosis is a relatively common lesion among diabetics – as it was detected among 45% of diabetic patients included in this study. We also found that the presence of diabetes and hypertension results in a significantly greater odds of hepatic arteriolosclerosis compared to those without diabetes or hypertension. This may indicate that development of a hepatic microangiopathy in diabetic patients occurs only in the presence of systemic hypertension but, as occurs in other organs like the kidney, it could also develop separately in diabetes and in arterial hypertension. While our analysis could not demonstrate this, we were limited by small numbers of patients with diabetes only (n=19) and hypertension only (n=28) and by the

close association between diabetes and hypertension. Whether diabetes or hypertension separately can lead to hepatic microangiopathy requires further investigation among a larger number of carefully selected patients.

Postulating that diabetics with hepatic arteriosclerosis would have a greater deposition of glycosylated proteins compared with non-diabetics with hepatic arteriosclerosis, we reviewed PAS stains (that can highlight deposited glycosylated proteins) and found a higher PAS-positivity in diabetic hepatic arteriosclerosis (43%) compared to non-diabetic hepatic arteriosclerosis (19%). This difference was of borderline statistical significance, which again may be due to small numbers of patients.

When present, hepatic arteriosclerosis involves >25% of portal tracts in most cases and has a patchy distribution. The patchy nature of findings may reflect varying numbers and sizes of portal tracts obtained by liver biopsy sampling, since these changes are only seen in terminal arterioles and difficult to recognize in or completely absent from larger vessels.

Hepatic arteriosclerosis as shown in our study is significantly associated with accompanying histopathology. Sinusoidal fibrosis, pericentral fibrosis, and a hyaline appearance of the portal collagen were findings that frequently accompanied hepatic arteriosclerosis. Of these findings, a hyaline appearance of the portal collagen was most frequent, followed by pericentral fibrosis, followed by sinusoidal fibrosis. The liver biopsy of 18 diabetic patients had all 4 findings (hepatic arteriosclerosis accompanied by concomitant sinusoidal fibrosis, pericentral fibrosis, and a hyaline appearance of portal collagen); while only 1 liver biopsy from a nondiabetic patient had all 4 findings present concomitantly. Harrison's group reported a similar constellation of sinusoidal fibrosis, pericentral fibrosis, and hyaline arteriosclerosis in a few of the patients included in their case-series. The coexistence of these histopathological findings suggests that "diabetic hepatosclerosis" may actually be a sequela of hepatic arteriosclerosis /microangiopathy of the liver and raises the question of whether hepatic arteriosclerosis in the liver is part of a sequence of events that may culminate in clinical complications – reminiscent of progression of histopathology seen in diabetic nephropathy.

Liver enzyme abnormalities or clinical complications associated with hepatic arteriosclerosis have yet to be determined. This study was designed to determine whether a microangiopathy of the liver is associated with diabetes and was not powered or designed to address this question. In our subgroup analysis we did not find any specific liver enzyme abnormality that correlate with the presence of hepatic arteriosclerosis. Given the dual blood supply to the liver (with two thirds of blood being supplied by the portal vein and one third from the hepatic artery), it would be unlikely that these hepatic arteriolar abnormalities would result in any liver test abnormalities in an otherwise normal liver. In this study patients with cirrhosis were deliberately excluded, as sinusoidal and pericentral fibrosis, and their zonal distribution would be difficult to evaluate at this stage. However, it is possible that liver abnormalities may be magnified in the cirrhotic or transplanted liver (or in an otherwise abnormal liver) that may be more sensitive to changes in the hepatic arterial circulation.

It is worth pointing out that the hepatic artery is the sole blood supply to bile ducts and therefore our finding of biliary abnormalities on histology in 19 of 66 patients with hepatic arteriolosclerosis is interesting. These biliary abnormalities included reactive biliary epithelium suggesting duct injury, loss of bile ducts, cholestasis, and ductular proliferation, with the latter being the most frequent (n=13). Fourteen of the 66 patients with hepatic arteriolosclerosis had associated elevations in serum alkaline phosphatase of which 7 had biliary histologic abnormalities. While one of the 14 cases was suspected to have drug toxicity, the remaining cases did not have a good explanation for an elevated alkaline phosphatase. This observation raises the question of whether biliary abnormalities may be a functional consequence of hepatic arteriolosclerosis and lead to increased alkaline phosphatase and cholestasis.

We also found that increasing age and female gender were independently predictive of hepatic arteriolosclerosis. Age is a well described risk factor for hyaline arteriolosclerosis in other end organs.(24) Female gender, though, is not a recognized predisposing factor for hyaline arteriolosclerosis in other end-organs and also requires further investigation. It is interesting that the risk of cardiovascular disease in women significantly increases after menopause, and increased risk of hyaline arteriolosclerosis in elderly women may represent a similar phenomenon (25).

We could not find a significant difference in the prevalence of diabetic hepatosclerosis (or any sinusoidal fibrosis) between the diabetic and nondiabetic group, a finding that had been postulated to be a marker of diabetic microvascular hepatopathy (17). Initial studies describing diabetic hepatosclerosis were small case studies without a control group and it is clear from our study that sinusoidal fibrosis, even in the absence of steatosis is not specific for diabetes. It is also possible that it could be reflective of severity of diabetes as previous case reports described diabetic hepatosclerosis in insulin-dependent diabetes with multiple complications. This is in contrast to the diabetic population studied in the present study that comprised 52% insulin-dependent patients and 56% with documented complications of diabetes. In fact, the five patients in our study with findings consistent with diabetic hepatosclerosis were insulin dependent type 2 diabetics with documented microvascular complications. All five of these patients had coexisting hepatic arteriolosclerosis and four of them had abnormal liver enzymes characterized by an elevation in alkaline phosphatase.

In summary, we describe a hyaline arteriolosclerosis of the liver among patients with diabetes and hypertension that is consistent with a hepatic microangiopathy, akin to the microangiopathy observed in the kidney and the retina. The most prominent finding is that of hepatic arteriolosclerosis, characterized by a hyaline thickening of the hepatic arteriolar walls, and associated with concomitant sinusoidal fibrosis, pericentral fibrosis, and hyaline appearance of the portal tracts in several diabetic patients. Besides diabetes and hypertension, other factors predictive of the presence of hepatic arteriolosclerosis are increasing age and female gender. There is some suggestion that hepatic arteriolosclerosis may lead to biliary injury and recognition of these changes on liver biopsies could be important. The clinical significance of this hepatic microangiopathy and its relationship to biliary injury require further study.

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Figure 1.

A. A normal portal tract (DPAS stain) showing hepatic arteriolar branches of caliber similar to bile ducts with no wall thickening or deposition of PAS positive material in the wall. The hepatic arteriolar wall is thin and constitutes less than $1/4^{\text{th}}$ of the thickness of the diameter. One can also note the slightly fibrillar characteristic of the portal collagen.

B. The enlarged portal tract in a diabetic patient showing arterioles showing hyaline arteriosclerosis, which was graded as mild. Also note that the bile duct shows mild reactive changes with uneven spacing of nuclei and size variation. (H & E stain).

C. The arteriolar wall shows moderate hyaline arteriosclerosis with hyaline material deposition in the wall. The bile duct included in the section appears normal. (H & E stain)

D. (trichrome stain). The arteriolar wall shows severe hyaline arteriosclerosis with $>1/2$ of the thickness of the arteriolar diameter (trichrome stain). All of the portal tracts in figures C–D also show hyalinization of the portal collagen.

Figure 2.

A. D-PAS stain showing mild staining in the arteriole with hyaline arteriosclerosis.

B. The arteriolar wall in another case shows intense staining of the hyaline material with PAS in the wall.

Figure 3.

A. Example of a case with hyaline arteriosclerosis (arrow) with loss of native bile duct, mild ductular reaction and elevated alkaline phosphatase. This patient had no other obvious explanation for the biliary changes.

B. Another example of a case with hyaline arteriosclerosis and showing bile duct with reactive epithelial changes showing uneven staining and placement of nuclei. Mild ductular reaction can also be seen at the periphery of the portal tract. Hepatic arteriosclerosis is also visible.

Figure 4.
Figure showing study flow.

Table 1

Histopathology	Grading
Fibrosis	Pattern and stage (Batts & Ludwig System)
Sinusoidal Fibrosis	Documented as absent/present and zone of involvement 1 to 3
Pericentral fibrosis	Documented as absent/present
Macrovesicular Steatosis	Mild (<33%), Moderate (33–66%), severe (>66%)
Steatohepatitis	Grade 1–3, Brunt System
Glycogenated nuclei	Mild (<5% cells), moderate (5–10%), or severe (>10%)
Lipogranulomas	Few (<5), Many (≥5)
Siderosis	Hepatocytic vs Kupffer cell; Grading 1–4 (Searle system)
Inflammatory activity	Batts and Ludwig system
Biliary Changes	Presence/absence of any biliary abnormality (reactive biliary epithelium, loss of bile ducts, ductular proliferation, cholestasis)
Hyaline fibrosis	Presence/absence of hyaline appearance (“smudgy”) of collagen in portal tracts
Hepatic hyaline arteriosclerosis	Thickening of the hepatic arteriole wall <ul style="list-style-type: none"> - Mild (wall thickness <1/3 of the diameter of the hepatic arteriole) - Moderate (wall thickness 1/3–1/2 the diameter of the hepatic arteriole) - Severe (wall thickness >1/2 of the diameter of the hepatic arteriole)
Distribution of hepatic hyaline arteriosclerosis	Graded based on number of involved portal tracts as 1 (<25%), 2 (25–50%), 3 (>50%)
Periodic Schiff Staining in vessels affected by hepatic hyaline arteriosclerosis	Graded subjectively as none, mild, moderate, severe

Table 2

a. Population Characteristics			
	Non-Diabetic N=89	Diabetic N=89	p-value
Demographics			
Age (years)	51 (10–88)	51 (13–83)	0.875
Male Sex	56% (50)	42% (43)	0.368
Co-morbidities			
BMI (kg/m ²)*	30 (19–43)	33 (20–54)	0.0039
HTN*	33% (28)	78% (68)	<0.0001
Dyslipidemia*	20% (17)	52% (42)	<0.0001
Smoking (ever)	42% (36)	31% (25)	0.125
Coronary Artery Disease*	7% (6)	22% (18)	0.004
Peripheral Vascular Disease*	1% (1)	14% (10)	0.003
Liver specific co-existing exposures			
Chronic hepatitis C infection	57% (50)	60% (51)	0.671
Chronic hepatitis B infection	10% (9)	6% (5)	0.285
Alcohol use (any)	24% (20)	22% (18)	0.712
Liver Enzymes			
AST (IU/L)	40 (6–1210)	45 (14–1030)	0.300
ALT (IU/L)	50.5 (6–1350)	46 (3–1210)	0.632
Alkaline Phosphatase (IU/L)	84 (32–482)	93 (30–762)	0.055
Total Bilirubin (mg/dL)	0.42 (0.12–24)	0.43(0.17–2.6)	0.892
Indication for Biopsy¹			
HCV Staging	55%	55%	0.620
HBV Staging	8%	5%	
NAFLD	11%	9%	
Abnormal liver enzymes	18%	20%	
Drug injury	2%	3%	
Jaundice	0%	2%	
Concern for Autoimmune Disease	2%	1%	
Other ²	3%	1%	

b. Characteristics of Diabetic Patients (n=89)		
Characteristic	Number of patients with available data	% (N)
Type 1 Diabetes Type 2 Diabetes	88	12% (11) 87% (77)
Hemoglobin A1C (median with range)	58	7.6% (4.6%–15.8%)
Insulin Use	85	57% (48)
Presence of any microvascular complication (nephropathy, retinopathy, or peripheral neuropathy)	58	53% (31)

b. Characteristics of Diabetic Patients (n=89)		
Characteristic	Number of patients with available data	% (N)
Presence of nephropathy (microalbuminuria, nephropathy, CKD, or ESRD)	49	37% (18)
Presence of retinopathy	38	18% (6)
Presence of peripheral neuropathy	51	41% (21)

c. Baseline Histological Characteristics			
Pathology	(-) DM N=89	(+) DM N=89	p-value
Stage of Fibrosis			
0	16.9% (15)	11.2% (10)	0.0936
1	22.5% (20)	37.1% (33)	
2	40.5% (36)	28.1% (25)	
3	20.2% (18)	23.6% (21)	
Pericentral Fibrosis	25.8% (23)	27.0% (24)	0.8650
Hyalinization of portal tracts	19.1% (17)	31.8% (28)	0.052
Steatosis*	40.5% (36)	59.6% (53)	0.0108
Steatohepatitis*	24.7% (22)	40.5% (36)	0.0252
Biliary changes	77.5% (69)	80.9% (72)	0.580
Glycogenated nuclei	29.2% (26)	37.1% (33)	0.2650
Lipogranulomas	15.7% (14)	13.5% (12)	0.6712
Kupffer cell siderosis	15.7% (14)	27.0% (24)	0.0674
Hepatocyte iron	6.7% (6)	7.9% (7)	0.773

Age, BMI, and liver enzymes are expressed as median with range.

¹ None of the included patients underwent liver biopsy for concern of biliary disease.

² Indication listed as “other” represents biopsies obtained for concern of infiltrative disease, sarcoidosis, Wilson’s disease, cirrhosis, or iron overload.

Table 3

Primary and Secondary Outcomes

Pathology	(-) DM N=89	(+) DM N=89	p-value
Primary Outcome			
Sinusoidal Fibrosis in absence of steatosis	7.9% (7)	5.6% (5)	0.550
Secondary Outcome			
Sinusoidal Fibrosis – Any	20.2% (18)	29.2% (26)	0.1645
Hepatic hyaline arteriosclerosis*	29.2% (26)	45.0% (40)	0.0298

Table 4

Associations between Hepatic Arteriolosclerosis and Demographic Variables/Co-morbidities

Variable	Total n	HA No n=112	HA Yes n=66	P-value
		% (n) or median (range)	% (n) or median (range)	
Age (years)	178	50 (10–88)	53 (12–83)	0.0079
Male Sex	178	58.9% (66)	40.9% (27)	0.0201
BMI (m/kg ²)	90	30 (19–54)	33(23–43)	0.3027
Diabetes	178	43.8% (49)	60.6% (40)	0.0298
HTN	173	47.3% (52)	69.8% (44)	0.0041
Dyslipidemia	166	29.3% (31)	46.7% (28)	0.0243
CAD	164	10.2% (11)	23.2% (13)	0.0252
PVD	159	3.9% (4)	12.7% (7)	0.0358
Chronic HCV infection	173	60.0% (66)	55.6% (35)	0.5682
Chronic HBV infection	174	7.3% (8)	9.4% (6)	0.6230
Smoking	166	62.6% (67)	64.4% (38)	0.8189
Alcohol (any)	166	79.1% (83)	73.8% (45)	0.4353

* Wilcoxon rank sum test was used to compare medians of continuous variables; chi square analysis was used to compare proportions of dichotomous variables.

Table 5

Univariate Logistic Regression: Predictors of Hepatic Hyaline Arteriosclerosis

Variable	Crude OR	95% CI	p-value
Age	1.030	1.006–1.055	0.0135
Female gender	2.072	1.117–3.847	0.0209
Diabetes	1.978	1.065–3.673	0.0308
HTN	2.583	1.341–4.975	0.0045
Dyslipidemia	2.117	1.097–4.086	0.0254
CAD	2.665	1.106–6.423	0.0289
PVD	3.646	1.018–13.057	0.0469
Smoking	1.080	0.558–2.093	0.8189
Alcohol	0.745	0.356–1.561	0.4361
BMI	1.011	0.950–1.076	0.7311

Table 6

Multivariate Logistic Regression Model Predicting HA (N =178)

Variable	Adjusted OR	95% Confidence Limits		P-value
Both diabetes & hypertension	2.551	1.142	5.697	0.0223
Diabetes only	2.064	0.625	6.818	0.2348
Hypertension only	2.040	0.735	5.659	0.1710
No diabetes or hypertension (ref)	1			.
Female	2.015	1.041	3.900	0.0375
Male (ref)	1			.
Age (continuous)	1.027	1.001	1.055	0.0434

Table 7

Association between Hepatic Hyaline Arteriosclerosis and other histopathology findings

Pathology	Hepatic Arteriosclerosis Absent (n=112)	Hepatic Arteriosclerosis Present (n=66)	p-value
Fibrosis Stage 1	28% (31)	33% (22)	0.1153
2	34% (38)	35% (23)	
3	20% (22)	26% (17)	
0(ref)	19% (21)	6% (4)	
Pericentral Fibrosis*	18% (20)	41% (27)	0.0008
Sinusoidal Fibrosis (Any)*	17% (19)	38% (25)	0.0018
Hyalinization of the portal tract*	8% (9)	55% (36)	<0.0001
Steatosis	48% (54)	53% (35)	0.5348
Steatohepatitis	31% (35)	35% (23)	0.6208
Biliary changes	16% (18)	29% (19)	0.0434
Glycogen nuclei	29% (33)	39% (26)	0.1740
Lipogranulomas	12% (13)	20% (13)	0.1399
Kupffer Cell Siderosis	19% (21)	26% (17)	0.2704
Heptocyte Iron	5% (6)	11% (7)	0.1936