REVIEW

DIABETIC HEPATOPATHY

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Abstract

Introduction: Simple steatosis or nonalcoholic steatohepatitis are liver diseases associated with diabetes mellitus (DM). However, a form of diabetic microangiopathy with hepatic sinusoidal fibrosis and basement membrane deposition without cirrhosis has been described and referred as diabetic hepatosclerosis (DH). Objective: To identify scientific studies and to deepen the knowledge on DH, and to evaluate the prevalence of DH in the main published studies in medical literature. Method: Integrative review of the literature conducted in the database PubMed/MEDLINE, and crossed the following descriptors from the Health Science Descriptors (DeCs) and MeSH: liver microangiopathy, hepatosclerosis and diabetes mellitus connected by the Boolean operator AND. Only studies that evaluated the prevalence of DH were selected, summarizing and identifying the limitations of research from 1965 to date. Results: The sample consisted of five studies published that met the inclusion criteria. Studies showed the following aspects: 1. Harrison SA, et al. (2006), described 12 patients identified from hepatic biopsy findings, all had a history of long-standing DM and a noncirrhotic form of hepatic sinusoidal fibrosis not associated with nonalcoholic steatohepatitis. 2. Chen G, et al. (2009), reported a prevalence of 12% in 10-year of study. 3. Hudacko RM, et al. (2009) showed that in autopsies from 57 adults with DM, only 1 case (1.7%) of DH was identified. 4. Wang Z et al. (2012), in their study showed that pathological features of 14.2% cases were consistent with the diagnosis of DH. 5. Balakrishnan M, et al. (2015) showed that DH was significantly more prevalent among diabetic patients compared with controls: 45% versus 29%. Conclusion: We identified a small number of studies that addressed the topic, and represent a hepatic form of microvascular disease in DM, in the majority of the cases clinically silent, probably it is common but under-recognized. There is a paucity of literature about DH, and further studies are needed to precisely characterize the DH, to understand mechanisms of pathogenesis and your clinical significance.

Keywords: Liver microangiopathy; Hepatosclerosis; Diabetes mellitus; Integrative review.

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INTRODUCTION

Simple steatosis or nonalcoholic steatohepatitis are liver diseases associated with diabetes mellitus (DM). The normal hepatic sinusoids, unlike other vascular beds, have no basement membranes to become thickened, as it happens in diabetic nephropathy, retinopathy, peripheral neuropathy, and skin diabetic ulceration. However, the sinusoidal fibrosis, even in the absence of typical features of nonalcoholic steatohepatitis or alcoholic hepatopathy has been suggested to be associated with diabetes, and are comparable to diabetic microangiopathy.[1] Thus, a form of hepatic sinusoidal fibrosis and basement membrane deposition without cirrhosis has been described and referred as diabetic hepatopathy (DH).[2]

The DH most often occurs in subjects with long-lasting type 1 DM or type 2 DM already accompanied by other end-organ damage, especially in kidney, and has been proposed to represent the hepatic manifestation of diabetic microangiopathy.[3]

The majority of the cases of DH are clinically silent, and the diagnosis is based in the histopathological patterns of lesions. However, the elevation of concentrations of alkaline phosphatase frequently found should be taken into account in the differential diagnosis of cholestasis in DM.

The purpose of this integrative review was to evaluate the prevalence of DH in the published studies in medical literature.

METHODS

We used the integrative review method, through studies of international literature. The methodology of this integrative literature review was based on Ganong's guidelines for conducting such a review.[4] This methodology include six tasks: selecting the hypotheses or research questions, sampling the research to be reviewed, representing the characteristics of the studies and their findings, analyzing the findings, interpreting the results, and reporting the results. Therefore, the integrative review allows the use of several types of studies to evidence a field of study.[5]

We selected studies that evaluated the prevalence of DH, in the format of scientific research, international, and published in English. We excluded scientific studies published in languages other than those established in the inclusion criteria, qualitative studies, literature reviews and case reports.

The search was conducted in July/2015 in the electronic database PubMed/MEDLINE, from 1965 to 2015, and crossed the following descriptors from the Health Science Descriptors (DeCs) and MeSH: liver microangiopathy, hepatosclerosis and diabetes mellitus connected by the Boolean operator AND. The main question established for this review was: What is the prevalence of DH? Searching the electronic database PubMed/MEDLINE, 9 studies were preselected; after reading all the titles and the abstracts, the final sample consisted of 5 studies, selected according to the inclusion and exclusion criteria.

RESULTS

From the data collection, characteristics, analysis and integrative synthesis of the studies were conducted.

The characteristics of the included studies used in the integrative review are outlined in table 1.

Table 1 - Characteristics of included studies

Database	Title of study	Journal	Authors	Language	Year
PubMed	Diabetic hepatosclerosis: diabetic microangiopathy of the liver.	Archives of Pathology & Laboratory Medicine	Harrison SA, Brunt EM, Goodman ZD, Di Bisceglie AM.[2]	English	2006
PubMed	Diabetic hepatosclerosis: a 10-year autopsy series.	Liver International	Chen G, Brunt EM.[6]	English	2009
PubMed	Diabetic microangiopathy in the liver: an autopsy study of incidence and association with other diabetic complications.	American Journal of Clinical Pathology	Hudacko RM, Sciancalepore JP, Fyfe BS.[7]	English	2009
PubMed	Clinicopathologic features of hepatic diabetic microangiopathy.	Zhonghua Bing Li Xue Za Zhi / Chinese Journal of Pathology	Wang Z, He QH, Yang L, Pang JX, Sun MJ, Yu Q, Liu DG.[8]	Chinese	2012
PubMed	Hepatic Arteriolosclerosis: A Small-vessel Complication of Diabetes and Hypertension.	American Journal of Surgical Pathology	Balakrishnan M, Garcia-Tsao G, Deng Y, Ciarleglio M, Jain D.[9]	English	2015

The study of Harrison, Brunt, Goodman e Bisceglie[2] showed the following results: Twelve diabetic patients with the hallmark histologic findings were gathered at Saint Louis University School of Medicine and the Armed Forces Institute of Pathology of USA. The patients were predominantly female (67%) and ranged in age from 28 to 68 years (mean age, 45.8 years) at the time of biopsy. Most of the patients had some evidence of end-organ damage from DM. On histologic examination of 14 biopsy specimens, 12 patients were identified from biopsy findings with DH; all had a history of long-standing DM and a noncirrhotic form of hepatic sinusoidal fibrosis not associated with nonalcoholic steatohepatitis. Most of these patients had substantial evidence of microvascular complications, including retinopathy, nephropathy, and peripheral and autonomic neuropathy. Alkaline phosphatase elevation was common. Liver biopsy specimens showed extensive dense perisinusoidal fibrosis, and immunostaining revealed basement membrane components in a perisinusoidal distribution. Features of nonalcoholic steatohepatitis were not present in the biopsy specimens.

In evaluation prevalence of DH in an autopsy series of diabetic patients, the study of Chen e Brunt[6] showed the following results: of 976 autopsies in the 10-year period, 159 DM was included in study. Nineteen cases (12%) met criteria of DH. The affected autopsy patients were more often men than women (14:5), mean age 56.4 years. Compared with an age- and gender-matched group of autopsied diabetic patients without DH, the DH group had a significantly higher percentage of diabetic nephropathy (89 *vs.* 47%).

The study of Hudacko, Sciancalepore e Fyfe BS [7] aimed to investigate the frequency of DH and its correlation with other diabetic microangiopathic complications. Complete autopsies of patients with diabetes performed at Robert Wood Johnson University Hospital, New Brunswick, NJ, between 1990 and 2007 were reviewed. The authors reviewed 57 complete autopsies of adult diabetic patients, including 30 men and 27 women, with an age range from 37 to 91 years. The diabetes was type 1 in 4 patients and type 2 in 39 patients. The type of diabetes was not specified for 14 patients. Of the 4 patients with type 1 DM, only 1 had DH and the remaining 3 had nonspecific findings in the liver. Of the 39 patients with type 2 DM, 5 had cardiac sclerosis, 4 had viral hepatitis, 9 had NAFLD, 21 had nonspecific findings in the liver, and none had HD.

The study of Wang[8] aimed to study the clinicopathological features of diabetic microangiopathy in liver and DH of elderly male with type 2 DM. The study analyzed 120 autopsy cases with T2DM (diabetic group) and contemporary 48 cases, non-diabetic and glucose tolerance abnormal, matched by gender and age (control group) were selected in the study. The microangiopathy was observed in 54.2% cases of diabetic group. Microangiopathy was seen in 16.7% cases of the control group. The fibrosis and sclerosis of portal areas were detected in 55.8% cases of type 2 DM group. The fibrosis and sclerosis of portal areas were detected in 22.9% cases of the control group. The end result showed that pathological features of 14.2% (17/120) cases were consistent with the diagnosis of DH.

A cross-sectional blinded study was conducted by Balakrishnan, Garcia-Tsao, Deng, Ciarleglio, Jain[9] with the specific aim of evaluating the association between hepatic sinusoidal fibrosis and hepatic arteriolosclerosis with diabetes. Liver biopsy findings from 89 diabetic patients were compared with those of 89 nondiabetic patients matched by age and hepatitis C virus infection status. Among diabetic patients, 87% had type 2 DM, and 57% used insulin, and DH was significantly more prevalent among diabetic patients compared with controls: 45% versus 29%. The presence of both diabetes and hypertension had a significant odds ratio for DH.

DISCUSSION

The hepatic disease associated with DM is common and usually takes the form of simple steatosis or nonalcoholic steatohepatitis. More recently, studies carried in liver biopsies of patients with DM observed a form of diabetic microangiopathy with hepatic sinusoidal fibrosis and basement membrane deposition without cirrhosis that was defined as DH.[3]

Through the presented results, it is observed that DH is the focus of only a few studies. However, there was an increase in researches when we consider those conducted in the last six years of this review. This review provides an evaluation of the prevalence of the DH, and the data revealed by this review may be of particular importance to the epidemiologic researcher, and to endocrinologists, in the sense that we can think about moving ahead in investigations of vascular alterations hepatic of diabetic patients.

The integrative review is a valuable method, because professionals do not usually have enough time to search the literature for all scientific knowledge on diabetic complications, and even carry out a critical analysis of the results of published studies.[5] For the topic studied, this type of research provides not only expanded knowledge but also a state-of-the-art synthesis and the detection of knowledge gaps for future analyses.

Hepatic abnormalities associated with DM have long been recognized that, and include from simple steatosis to nonalcoholic steatohepatitis, cirrhosis, insulin-induced hepatic glycogenosis and Mauriac syndrome.[10] In addition, there is an association between obesity, DM, and hepatocellular carcinoma. [11] To date, there have been few clinical or pathology texts that describe lesions as DH.

DH is a marker of severe DM, its pathogenesis is of metabolic origin due to prolonged hyperglycemia and increased of advanced glycation end products, leading to enhanced lipid peroxidation, with their byproducts inducing vasoconstriction and increasing platelet adhesion and aggregation, which ultimately results in basement membrane and small artery thickening .[12] It was initially diagnosed in 2 small series from the 1980s and a case report describing sinusoidal fibrosis, in which authors noted the lesion to be comparable to diabetic microangiopathy.[1,13]

As the entire body of knowledge about DH is based on histological data, the clinical relevance is unclear. The clinical presentation is variable, with symptoms such as full-blown cholestasis, secondary to mechanical compression or ischemia of the biliary ducts caused by perisinusoidal fibrosis. [2,6,7] Laboratory tests may present a cholestatic pattern, with high levels of bilirubin (especially direct bilirubin), Gamma glutamyl transferase, and alkaline phosphatase.[14] Thus, DH should be taken into account in the differential diagnosis of cholestasis in DM.

While improved glycemic control has been shown to prevent diabetes-related microvascular renal and neuropathic complications both in humans with type 1 DM and in animal models of diabetes, it has yet to be determined whether DH can be prevented by intensive glycemic control.[15]

Although it seems that DH occurs in patients with type 1 DM more often than type 2 DM, the true prevalence of the lesion is still unknown. In this integrative review the prevalence has varied from 1.7% to 45.0%, possibly in dependence upon duration of DM, of the patient characteristics, and differences in study designs. The risk of developing DH or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia. Hypertension, hypercholesterolemia, hyperuricemia, and genetics also promote the development of angiopathy, in addition to hyperglycemia, and in patients with DH the 3 major risk factors associated with the development of microangiopathy are hyperglycemia, hypertension, and hyperlipidemia.[16] Of the studies evaluated only one[9] evaluated the clinical data, diabetes treatment, and comorbidities at the time of biopsy (eg, hypertension, dyslipidemia). Different study designs provide information of different quality. A well-designed study will clearly identify an exposure and an outcome in an objective, quantifiable manner to answer a defined hypothesis. [17] Of the 5 studies evaluated in this review, 2 case-control studies and 3 retrospective studies were included. The variation of results can be explained by research design, and sample size.

CONCLUSION

We identified a small number of studies that addressed the topic, and represent a hepatic form of microvascular disease in DM, in the majority of the cases clinically silent, probably it is common but under-recognized. There is a paucity of literature about DH, and further studies are needed to precisely characterize the DH, to understand mechanisms of pathogenesis and your clinical significance.

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