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Prevalence of Liver Cirrhosis and Its Association with Obesity Among Hispanics and Mexican Americans: An Evidence Synthesis

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ABSTRACT

INTRODUCTION
The obesity epidemic is a growing public health concern. In addition to the already known complications and comorbidities associated with obesity, data suggest that obesity is an independent risk factor for the development of liver disease.[1,2] However, there is a paucity of data regarding the clinical correlation of obesity and cirrhosis in a predominantly Hispanic population of South Texas. The aim of this systematic literature review is to investigate the prevalence of cirrhosis stratified by obesity in Hispanic populations.

MATERIALS AND METHODS
PubMed was used to perform a thorough literature search. The terms liver cirrhosis and obesity were combined with the subheading's epidemiology, genetics, and complications. The articles generated were then filtered by human species, full text, and date range 2000-2020. Pediatric studies and systematic reviews were excluded. Articles were then evaluated for relevance and studies not pertaining to our population in question were excluded.

RESULTS
Obesity is an independent risk factor for developing cirrhosis in Hispanic populations and increases the morbidity and mortality burden in this demographic. A higher prevalence of obesity was found in the regions of Mexico that have the highest mortality rates from liver cirrhosis. Therefore, it is reasonable to extrapolate and estimate similar trends in American towns across the US-Mexican border. Studies have found that an increased prevalence of cirrhosis in Hispanics in South Texas compared to the general US population.

DISCUSSION
There is an increased prevalence of cirrhosis in Hispanics compared to other races/ethnicities in the United States. Moreover, obesity increases the risk of developing liver fibrosis and cirrhosis. It is important to establish the relationship between obesity and liver cirrhosis in Hispanics living in South Texas to properly allocate resources to further alleviate the burden of disease.

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MANUSCRIPT

INTRODUCTION

Chronic liver disease is the 5th leading cause of death in the United States of individuals between ages 45-54.[1] Moreover, it is the 6th and 7th leading cause of death in Hispanic men and Hispanics, respectively.[1] An estimated 1.7% of Americans aged 18 and over have liver disease.[2] In contrast to other causes of liver disease, the prevalence of nonalcoholic fatty liver disease (NAFLD) has been growing as is diabetes and obesity.[3] The prevalence is higher in non-Hispanic blacks, Mexican Americans, and those living below the poverty level.[2] The prevalence of obese adults in Hidalgo County, South Texas is higher than the state of Texas, 42.9% versus 29.2%, respectively.[4] This suggests that there are clinical and demographic disparities between individuals that increase risk of developing cirrhosis. Our knowledge of the epidemiology of liver disease in Mexican Americans is limited and needs further exploration to assess the burden of disease in this population.[5]

The differences in incidence, rates of progression, and mortality of liver cirrhosis have been observed among ethnically diverse populations.[6–8] Hispanic patients are more likely to be diagnosed with cirrhosis at an age less than 40 than African Americans.[6] Although the average body mass index (BMI) and prevalence of diabetes mellitus type II is similar between Hispanic and African American patients, Hispanics are more susceptible to NAFLD than African Americans.[7]

In addition to the other known complications and comorbidities associated with obesity, an increased BMI is an independent risk factor for decompensation of liver cirrhosis and recognized as a risk factor for NAFLD. [9–11] Metabolic syndrome is a disease characterized by obesity/increased BMI, elevated blood pressure, elevated triglycerides, and elevated blood glucose levels. NAFLD is the hepatic manifestation of this disorder, resulting in the accumulation of triglycerides and fatty acids within the liver parenchyma.[12] NAFLD can progress to cirrhosis and eventually end-stage liver disease.[12] Of those with NAFLD, an estimated 40-100% of patients are obese.[13] Leading hypotheses suggest liver tissue injury in the setting of NAFLD is the result of adipose deposition and subsequent activation of adipokines (e.g., IL-6, TNFa), which cause a variety of effects on the surrounding liver tissue including inflammation, oxidation, angiogenesis, and fibrosis.[12] Along with NAFLD, cirrhosis is well known to result from alcoholism, hepatitis C virus infection, hepatitis B virus infection, inherited diseases, idiopathic, a combination of known factors, or cryptogenic causes.[14]

Genetic factors also play a role in the risk of developing cirrhosis/advanced liver fibrosis. A specific focus related to NAFLD and liver disease is the patatin-like phospholipase domain-containing-3 (PNPLA3) gene and two of its single nucleotide polymorphisms (SNPs), rs738409 and rs2281135.[15–18] These SNPs have been associated with hepatic fat content as well as increased hepatic aminotransferase levels.[15–20] A study by Valenti and colleagues even reported a definitive association between the PNPLA3 rs738409

SNP and the development of cirrhosis/advanced liver fibrosis in patients with NAFLD.[21] There is also evidence suggesting that Hispanics have a higher frequency of these genetic variants compared to other ethnicities, which coincides with increased prevalence of NAFLD in this population.[18]

Cirrhosis and its sequelae have high rates of morbidity and mortality with a significant burden of disease. Hepatocellular carcinoma (HCC) is a well-known complication of liver cirrhosis with increasing incidence in the United States especially among Hispanics and blacks.[22,23] The yearly age-adjusted incidence rate in Hispanics were 1.2 times higher than in blacks and 2.7 times higher in non-Hispanic whites.[22] Furthermore, the incidence of HCC among Latinos in South Texas is highest in the United States.[24] These findings may be attributable to increasing incidence of obesity, NAFLD and insulin resistance.

Access to healthcare and acculturation of ethnic and racial minorities may also increase the prevalence and burden of liver cirrhosis among Mexican Americans living in South Texas. However, there is a paucity of data regarding the prevalence of liver cirrhosis for Hispanics and Mexican Americans in South Texas. Identifying and summarizing relevant publications in these populations can help estimate the burden of disease in the South Texas, identify gaps in knowledge and research relevant to this population, inform better resource allocation. The aim of this literature review is to investigate the prevalence of cirrhosis in Hispanic populations and its relationship with known risk factors including obesity and diabetes mellitus type II.

MATERIALS AND METHODS

PubMed was used to perform a thorough literature search. The terms “liver cirrhosis” and “obesity” were combined with the subheading's “epidemiology,” “genetics,” and “complications.” The articles generated were then filtered by the human species, full text, and date range 2000-2020 which resulted in 140 studies. We then excluded pediatric studies and systematic reviews which narrowed our relevant material to 115 studies. No language restrictions were applied. Two independent reviewers then evaluated articles for relevance and studies not pertaining to the population in question were excluded.

Mesh search methodology:
(("Liver Cirrhosis"[Mesh]) AND "Body Mass Index"[Mesh]) AND "Obesity"[Mesh] Filtered: human species, full text, date range 2000-2020

We included studies that investigated the association of cirrhosis and obesity or other metabolic factors in Hispanic and Mexican American populations. Data related to liver cirrhosis and obesity were analyzed and included prevalence of cirrhosis within respective populations, BMI, waist circumference, HDL levels, fasting glucose levels, and mortality from cirrhosis.

RESULTS

In a cohort of Hispanic patients in South Texas, the prevalence of cirrhosis/fibrosis was estimated to be 3.54% using the AST to platelet ratio index (APRI).[25] When comparing patients with APRI>1 and those with APRI <1, average BMI and waist circumference were associated with cirrhosis/advanced fibrosis ($p=0.002$ and $p<0.01$, respectively).[25] The study also found that central obesity was an independent risk factor for cirrhosis/advanced fibrosis ($p=0.04$) and that 65.3% of cirrhosis/advanced fibrosis could be explained by obesity in this cohort.[25]

In obese Hispano-American patients undergoing gastric bypass, 30.9% had some degree of liver fibrosis, of which 6.9% had moderate to severe fibrosis as defined by the Kleiner-Brunt classification system.[26] In the Hispanic group, 58% had NAFLD and 35% had liver fibrosis.[26] Additionally, compared to patients

with none to moderate fibrosis, those with moderate to severe fibrosis had a statistically significant higher average BMI at 0, 6 months, and 1 year ($p<0.001$).[26]

Gutierrez-Grobe and colleagues found that the prevalence of liver fibrosis was 48.8% in patients with NASH.[27] Individuals who were metabolic healthy obese (MHO) had statistically significant lower prevalence of significant fibrosis compared to metabolic unhealthy obese (MUHO) individuals ($p=0.001$) as evaluated by NAFLD scores.[27] Non-significant fibrosis was also lower in MHO compared to MUHO individuals ($p=0.05$ using the Katzmarzyk, Hamer, Ortega, Irace, and Khan criteria and $p=0.0001$ using the Song and Consensus criteria).[27] When using transient elastography, MHO individuals had lower levels of advanced liver fibrosis versus MUHO individuals ($p<0.05$).[27] Further evaluation of various components of metabolic syndrome revealed that individuals with lower levels of HDL had higher prevalence of liver fibrosis compared to those with higher levels of HDL (OR 2.14, $p=0.03$).[27] Furthermore, those with higher fasting glucose levels had increased risk of advanced fibrosis estimated by NAFLD score than those with lower fasting glucose levels (OR 4.4, $p<0.05$).[27] In this study, fibrosis measured by APRI did not differ between MHO and MUHO patients.[27] Furthermore, a cross-sectional study of Mexican women with obesity revealed that obese women with NAFLD had increased waist circumference, higher fasting glucose levels, and higher triglycerides compared to obese women without NASH ($p=0.000$).[28]

In an ecological study in Mexico, researchers analyzed the change in prevalence of overweight and obese individuals between 1993 and 2000 across four different regions, North, Central, South, and Mexico City.[13] The mortality rates due to liver cirrhosis from 1990-2001 in those four regions were also analyzed.[13] It was found that all regions experienced increased mortality from liver cirrhosis with statistically significant findings in the South and North regions ($p<0.0001$).[13] While the prevalence of overweight individuals increased in all regions, obesity only increased in the Central and Mexico City regions.[13] The change in prevalence of overweight and obesity was only statistically significant in the South ($p=0.03$).[13] This could indicate that there is a link between increased obesity and increased liver cirrhosis mortality.

DISCUSSION

These researchers conducted a systematic search strategy to identify and synthesize available evidence regarding the relationship between liver cirrhosis and obesity. Two researchers manually reviewed the literature for relevance and applied the inclusion and exclusion criteria. The aim of this evidence synthesis is to assess the association between liver cirrhosis and obesity among Mexican Americans and Hispanics.

Overall, we observed that obesity is reported as an independent risk factor for the development of liver cirrhosis.[13,25,27] Not only was obesity a risk factor, but Jiao et al. found that 65.3% of cases with individuals with cirrhosis and advanced fibrosis may be attributable to obesity alone in their cohort of Hispanic patients.[25] Data suggest that obesity is associated with conditions that lead to the development of cirrhosis or nonalcoholic fatty liver disease, such as insulin resistance, dyslipidemia, and other cardiometabolic risk factors.[9–11] Interestingly, patients with higher degrees of liver fibrosis also may have worse post-operative outcomes following Roux-en-Y gastric bypass than patients with lower degrees.[26] Specifically, these patients haver higher BMIs at 6 months and 1 year post-Roux-en-Y gastric bypass than those with less or no fibrosis.[26] Thus, not only is obesity a risk factor for the development of cirrhosis, but cirrhosis may also portend worse weight loss outcomes.

Studies suggest that not all patients who are obese have similar outcomes, which may be attributable to differing metabolic features.[27,29,30] Patients referred to as ‘metabolically healthy obese’ (MHO) do not have the metabolic burden, such as impaired insulin sensitivity, hypertension, dyslipidemia, and systemic inflammation, as those who are metabolically unhealthy obese (MUHO).[29] For example, patients that are MHO have comparable risk of developing cardiovascular disease to non-obese individuals, whereas

patients that are MUHO have increased risk of cardiovascular disease.[29] Gutierrez-Grobe and colleagues compared the presence of fibrosis amongst patients with MHO and MUHO in a Hispanic cohort and found MHO patients had a statistically significant lower prevalence of liver fibrosis that MUHO on transient elastography.[27] The APRI score was not a sensitive marker of MHO vs MUHO in one of the studies.[27]

Higher cirrhosis mortality rates have also been linked to obesity. Mendez-Sanchez et al. examined obesity and liver disease mortality in various regions of Mexico over a 17-year period and found that higher mortality rates due to liver cirrhosis occurred with increased rates of obesity.[13] This indicates a positive correlation between obesity and mortality rates. As previously mentioned, several factors may contribute to increase in mortality rates seen in patients with liver cirrhosis, such as increased prevalence of NASH and an aging population of patients with Hepatitis C infection.[2,31] Since South Texas is home to many individuals of Hispanic origin and has high rates of obesity, this area may be vulnerable to poor health outcomes related to liver cirrhosis and advanced fibrosis.[2,32]

This study has several limitations. Specifically, the findings are limited by the paucity of relevant research. Thus, more studies are needed to evaluate the impact of obesity on liver cirrhosis for Hispanic and Mexican American populations. The populations analyzed in this evidence synthesis were Hispanic and Mexican Americans. It would be interesting to determine if similar findings are seen in populations of different ethnic or racial backgrounds. Since two researchers reviewed relevant research and applied the inclusion and exclusion criteria, it is possible that some studies were missed and therefore, not included in our analysis.

This evidence synthesis of the literature found a positive correlation between prevalence of obesity and cirrhosis/advanced liver fibrosis among Hispanics and Mexican Americans. Hispanic patients that are obese have an increased risk of liver disease incidence, severity, and eventual mortality.[13,25,26,28] There is a heavy burden of disease in patients with cirrhosis and advanced liver disease.[31] Allocation of resources to this vulnerable population in South Texas are warranted, such as through education, research, and healthcare access, to reduce the overall burden of liver disease.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

First authorship	Alexa Perlick
Senior authorship	Jose Campo Maldonado, MD
Equal contribution	Abaigeal Thompson, Angel Rendon, Colton Wayne

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