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Are there ethnicity-based differences in the evaluation of individuals with abnormal liver biochemistries?

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Abstract

Background/Aims—Recent studies suggested NAFLD is less infrequent in African Americans (AA) than in Caucasians but it is unclear if this difference is biological or due to under-recognition/ under-referral. This study examined if there is an ethnicity-based difference in obtaining liver biochemistries or evaluating abnormal liver biochemistries by primary care physicians.

Methods—This study consisted of 45,016 AA and 49,660 Caucasians seen at our primary care clinics over a 3-year period. From these two groups, we identified patients with elevated aminotransferases (AA: 3,676, Caucasians: 4,644) and elevated bilirubin (AA: 1,295, Caucasians: 1,199) based on predefined criteria. Subsequently, we assessed the proportion of patients in each group who had liver-specific evaluation (viral serologies, abdominal imaging or GI clinic visit).

Results—Among patients with elevated aminotransferases, compared to Caucasians, AA did not have lower testing for viral hepatitis (26% vs. 25%), imaging (16% vs. 13%) or GI clinic visits (17% vs. 17%). Similarly, we did not observe clinically significant difference in the evaluation of elevated bilirubin between AA and Caucasians (viral serologies: 22% vs. 22%; imaging: 25% vs. 27%; GI clinic: 15% vs. 21%).

Conclusion—Under-recognition and under-referral are not likely to explain the reported ethnic differences in the prevalence of NAFLD.

Keywords

Aminotransferase; Charlson Index; Fatty liver

Introduction

Recent studies have shown that ethnicity-based differences exist in the prevalence of nonalcoholic fatty liver disease and cryptogenic cirrhosis(1-4). Caldwell et al., initially observed that individuals of primarily African-American descent are infrequently represented among their patients with NASH and cryptogenic cirrhosis, despite their overrepresentation among patients with major risk factors for NASH such as obesity and diabetes(1). Based on these observations, authors concluded that this phenomenon could result from under-recognition, under-referral or a true lower prevalence of NAFLD among African-Americans (1). Subsequently, two clinic-based studies showed that African-American patients are

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significantly underrepresented among patients with biopsy-proven NAFLD and cryptogenic cirrhosis(3;4). A recent population-based study by Browning et al., evaluated the prevalence of fatty liver disease using magnetic resonance technique. In this study, there existed a significant ethnic difference in the prevalence of NAFLD among 2,287 subjects chosen from a multiethnic, population-based Dallas Heart Study sample(5). This finding suggests a biological basis for lower prevalence of NAFLD in African-Americans, but more population-based studies are needed to examine if the observed ethnic difference in the prevalence of NAFLD is truls a biological phenomenon or a consequence of under-recognition and under-referral. Therefore, we conducted this study to examine if there is a systematic ethnic-based difference in obtaining liver biochemistries or evaluation of abnormal liver biochemistries in a primary care setting.

Methods

This database study was reviewed and received an exempt status by the Institutional Review Board at Indiana University School of Medicine. Data were collected from a large academic medical practice located in Indianapolis, which uses the Regenstrief Medical Record System (RMRS). The details of RMRS are discussed extensively elsewhere (6). In brief, this electronic record system captures patient information from three hospitals on the Indiana University Medical Center campus (Wishard Memorial Hospital, Indiana University Hospital, and Riley Hospital for Children) and from 30 primary care clinics scattered around the inner city of Indianapolis(6). This database links patient's medical history, laboratory test results, imaging and subspecialty clinic visits using a unique patient identifier.

Using the RMRS, we identified African-American and Caucasian patients seen at our Wishard primary care clinics from January 1, 2000 to December 31, 2003. From these two groups of patients, we further identified individuals who had aminotransferases and serum total bilirubin levels measured at least two times over a 12-month period after their first visit during the study period. From those who had aminotransferases and serum total bilirubin measured at least two times, we identified those who had abnormal aminotransferases and abnormal serum total bilirubin. Elevated aminotransferases were defined as AST > 40 IU/L and/or ALT >35 IU/L at least on two separate measurements over a 12-month period, and elevated bilirubin was defined as total serum bilirubin > 1 mg/dl at least on two separate measurements over a 12-month period. The upper limit of normal values for serum AST, ALT and total bilirubin for our laboratory were 40 IU/L, 35 IU/L and 1 mg/dl respectively. Ethnicity is self-reported and was available on 94% of patients seen during the study period.

In order to examine if there was a systematic ethnicity-based difference in the evaluation of patients with elevated aminotransferases and serum bilirubin in a primary care setting, we examined the proportion of African-American and Caucasian patients with elevated serum aminotransferases and serum bilirubin who had further liver-specific evaluation. The surrogate parameters used to measure the liver-specific evaluation included: (a) proportion of patients who had viral serologies (hepatitis C antibody and hepatitis B surface antigen) measured within 6 months after second abnormal AST or ALT or bilirubin measurement, (b) proportion of patients who had liver imaging (ultrasound or CT abdomen) within 6 months after second abnormal AST or ALT or bilirubin measurement and (c) proportion of patients who were seen in the gastroenterology clinic within 12 months after second abnormal AST or ALT or bilirubin measurement. Although study cohort consisted of patients seen during 2000-2003, their medical records were reviewed until mid-2004 to complete data extraction.

As patient's co-morbidities may influence physicians' clinical decision making in terms of obtaining liver biochemistries or conducting further evaluation in case of abnormal test results, we assessed Charlson and modified Charlson indices as surrogate measurements for the burden

of co-morbidities. The Charlson Index contains 19 categories of co-morbidity, which are primarily defined using ICD-9-CM diagnoses codes (a few procedure codes are also employed (7). Each category has an associated weight which is based on the adjusted risk of one-year mortality. The overall co-morbidity score reflects the cumulative increased likelihood of one-year mortality; the higher the score, the more severe the burden of co-morbidity(7). This index measures the burden of co-morbidities based on inpatient hospitalizations. We have also measured the modified Charlson index to take inpatient hospitalizations and outpatient clinic visits into account(8). The general estimation of alcohol consumption was made indirectly based on alcohol-related discharge diagnoses (e.g., alcoholic hepatitis, alcohol withdrawal, alcoholic liver disease, alcoholism, alcohol intoxication), detectable blood alcohol level, and selected inpatient and outpatient ICD9 codes (303.00, 303.9, 305.00, 291).

Data validity procedures, database management, and statistical analyses were performed using SAS software. Basic descriptive statistics, including means, standard deviations (SD), ranges, and percentages were used to characterize the study patients. Chi-xSquare tests for categorical variables and Student's t tests for continuous variables were used for univariate comparisons between African Americans and Caucasians. Multivariate logistic regression analyses were conducted on the cohort consisting of African Americans and Caucasians with abnormal liver biochemistries (8,320 with elevated aminotransferases and 2,338 with elevated bilirubin) to examine the relationship between selected variables (ethnicity, gender, weight, insurance status and modified Charlson index) and liver-specific evaluation. A p-value < 0.05 was considered statistically significant.

RESULTS

During the study period (1/1/ 2000-12/31/03), 45,016 African Americans and 49,660 Caucasians were seen in our primary care clinics. The demographics and the clinical characteristics of these two groups are shown in Table 1. There were no clinically significant differences in the demographics, burden of co-morbidities or frequency of bilirubin or aminotransferase measurements between two groups (Table 1). The health insurance status is shown in table 1 and there were no clinically significant differences between two groups. For those with at least two sets of liver biochemistry measurements, mean duration between measurements was 63 ± 90 days for African American and 70 ± 92 days for Caucasian patients.

Based on predefined criteria, 3,676 African Americans (31% of those who had≥2 measurements) and 4,644 Caucasians (34% of those who had≥2 measurements) had elevated aminotransferases. The clinical characteristics, co-morbidity burden, health insurance status of African Americans and Caucasians with elevated aminotransferases were comparable as shown in Table 2. The details of liver-specific evaluation in African Americans and Caucasians with elevated aminotransferases are shown in Table 2. The viral serologies were obtained in 26% of African Americans and 25% of Caucasians ($p=0.8$) and GI clinic visits occurred in 17% of African Americans and 17% of Caucasians ($p=0.9$). Abdominal imaging was obtained in 16% of African Americans and 13% of Caucasians. Although this difference was statistically significant in favor of AA having more abdominal imaging ($p<0.001$), it does not appear to be clinically significant. Liver biopsy data were not available.

Based on predefined criteria, 1,295 African Americans (12.3% of those who had≥2 measurements) and 1,199 Caucasians (10.2% of those who had≥2 measurements) had elevated total bilirubin. The clinical characteristics, co-morbidity burden, health insurance status of African Americans and Caucasians with elevated serum bilirubin were comparable (Table 3). The details of liver-specific evaluation in African Americans and Caucasians with elevated serum bilirubin are shown in Table 3. The viral serologies were obtained in 22% of African Americans and 22% of Caucasians ($p=0.9$) and abdominal imaging obtained in 25% of African

Americans and 27% of Caucasians (p=0.3). However, compared to Caucasians, significantly lower proportion of African Americans with elevated bilirubin were seen in the GI clinic (15% vs. 21%, p<0.001). Liver biopsy data were not available.

The results of multivariate analyses showing the relationship between 5 selected variables (age, gender, weight, insurance status and modified Charlson index) and liver specific evaluation in patients with elevated aminotransferases are shown in Table 4. In general, modified Charlson index and age were the only two variables associated with liver specific evaluation in patients with elevated aminotransferases (Table 4). A similar pattern of independent association was observed between liver specific evaluation and modified Charlson index and age in patients with elevated serum bilirubin. Patients with modified Charlson index ≥ 4 were significantly more likely to have liver specific evaluation than those patients with modified Charlson index 0-3. Similarly, patients with age in the first three quartiles were significantly more likely to have liver specific evaluation than patients in the fourth quartile (Table 4).

DISCUSSION

In this study we did not find a systematic ethnicity-based difference in obtaining liver biochemistries or work-up of patients with abnormal liver biochemistries in a primary care setting. Although a greater proportion of Caucasian patients with elevated serum total bilirubin were seen in the GI clinic for further evaluation (Caucasians 21% vs. African American 15%, p<0.001), this was an isolated difference and it does not appear to be clinically significant. Overall, our study provides indirect evidence that under-recognition and under-referral are unlikely to explain the reported ethnic difference in the NAFLD prevalence. Our findings are in agreement with the study by Browning et al. which consisted of 2,287 adults participating in the Dallas Heart Study (5). In this study, African Americans had significantly lower prevalence of nonalcoholic hepatic steatosis compared to Caucasians as measured by the MR spectroscopy (24% vs. 33%, p<0.001). As it was a population-based study, this difference cannot likely be explained by a selection bias. It is not clear why African Americans have lower prevalence of NAFLD as they do not seem to have lower prevalence of risk factors for NAFLD such as obesity, diabetes and metabolic syndrome.

There are some limitations to our study. First, this is a retrospective study of electronic medical record system and thus carries the drawbacks of any retrospective study. Although study groups and outcomes have been carefully defined, one cannot entirely exclude unrecognized differences between the study groups. However, one might argue that retrospective studies are better suited to address questions dealing with physician practice patterns as the knowledge of an ongoing prospective study might modify their practice pattern (“Hawthorne effect”). Furthermore, prospective studies with required sample size to answer questions of this nature may not be practical. Second, it should be pointed out that our study does not directly address the ethnic differences in the prevalence of NAFLD but it addresses the fundamental question if there is a systematic difference in obtaining liver biochemistries or evaluating abnormal results by the primary care physicians. The precise diagnosis of NAFLD requires demonstration of fatty infiltration by imaging or by histology. However, we could not obtain liver histology and abdominal imaging findings from the electronic medical record system due to database restrictions, and we were unable to review individual medical records to retrieve these findings due to IRB stipulations. Finally, as the majority of our patients were uninsured, our study may not reflect a typical community practice where significantly greater number of patients carry commercial insurance. Despite these limitations, our study consisting of a large sample of patients shows that there does not appear to be a systematic ethnicity-based difference in obtaining liver biochemistries or in evaluating patients with abnormal liver biochemistries in a community-based primary care setting. Our study is not necessarily specific for NAFLD and thus our findings can be generalized to diagnosis and management of liver disease by health

care providers in the primary care setting. Our findings in conjunction with those by Browning et al., support a biological basis for lower prevalence of NAFLD in African Americans in the United States. Further studies are needed to investigate the biological basis for this observation.

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Abbreviations

NAFLD, Nonalcoholic Fatty Liver Disease; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; AA, African Americans.

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TABLE 1

Clinical Characteristics of African-American and Caucasian patients seen at our primary care clinics between January 2000-December 2003

	African-Americans (n=45,016)	Caucasians (n==49,666)
Age (yrs)	38.5 ± 19	40 ± 17
Female (%)	63	60
Weight (lbs)	177 ± 68	174 ± 64
Proportion with alcohol consumption (%)	6	6
Charlson Index†	2.1 ± 1.8	2.05 ± 1.62
Adjusted Charlson Index†	1.6 ± 1.4	1.5 ± 1.2
Insurance Status (%)		
- Private	5.2	4.6
- Medicare	16	13.5
- Medicaid	8.3	7
- Wishard Advantage*	16	24
- Uninsured	54	50
Patients who had ≥ 2 AST or ALT measurements (%)	11,715 (26%)	13,797 (28%)
Serum AST (IU/L, mean± s.d.)	39 ±69	35± 67
Serum ALT (IU/L, mean± s.d.)	34± 63	36± 69
Serum bilirubin (mg/dl, mean± s.d.)	0.7± 1.4	0.3± 1.4
Patients with abnormal AST or ALT (%)	3,676 (31%)**	4,644 (34%)**
Patients who had ≥ 2 bilirubin measurements (%)	10,553 (23%)	11,799 (24%)
Patients with abnormal bilirubin (%)	1,295 (12%)***	1,199 (10%)***

† Charlson and Adjusted Charlson Indices are co-morbidity scores and they provide an indication of co-morbidity burden (7; 8).

* Wishard Advantage is a hospital sponsored managed care program for low income residents of Marion County, Indiana.

** This value represents the proportion of patients with ≥ 2 AST or ALT measurements who had elevated aminotransferases.

*** This value represents the proportion of patients with ≥ 2 bilirubin measurements who had elevated serum bilirubin values.

Table 2

Characteristics of African-American and Caucasian patients with abnormal aminotransferases and the details of their work-up[1]

	African-Americans (n=3,676)	Caucasians (n=4,644)
Age (yrs)	49 ± 15	48± 13
Female (%)	44	46
Weight (lbs)	189 ± 58	195 ± 58
Charlson Index[2]	0.5 ± 1.4	0.4 ± 1.2
Adjusted Charlson Index[2]	1.0 ± 1.8	0.8 ± 1.4
Died within 12 months (%)	13	9
Lost to follow-up (%)	2.7	2.8
Insurance Details (%)		
- Private	5.7	5.45
- Medicare	16	13.35
- Medicaid	7.3	5.38
- Wishard Advantage[3]	20	25.4
- Uninsured	51	50.37
Proportion who had viral serologies obtained (%)	26	25
Proportion who had abdominal imaging obtained (%)	16	13
Proportion seen in the GI Clinic (%)	17	17

[1] Data are presented as mean ± sd unless specified otherwise

[2] Charlson and Adjusted Charlson Indices are co-morbidity scores and they provide an indication of co-morbidity burden (7; 8).

[3] Wishard Advantage is a hospital sponsored managed care program for low income residents of Marion County, Indiana.

Table 3

Characteristics of African-American and Caucasian patients with abnormal serum bilirubin and the details of their work-up[1]

	African-Americans (n=1,295)	Caucasians (n=1,199)
Age (yrs)	46 ± 20	46± 17
Female (%)	43	41
Weight (lbs)	170 ± 75.5	176 ± 69
Charlson Index[2]	0.8 ± 1.6	0.7 ± 1.5
Modified Charlson Index[2]	1.1 ± 1.9	1.1 ± 1.7
Insurance Details (%)		
- Private	10.3	11
- Medicare	8.4	6.7
- Medicaid	8.4	5.4
- Wishard Advantage[3]	16.1	18
- Uninsured	57	60
Proportion who had viral serologies obtained (%)	22	22
Proportion who had abdominal imaging obtained (%)	25	27
Proportion seen in the GI Clinic (%)	15	21

[1] Data are presented as mean ± sd unless specified otherwise

[2] Charlson and Adjusted Charlson Indices are co-morbidity scores and provide an indication of co-morbidity burden (7; 8).

[3] Wishard Advantage is a hospital sponsored managed care program for low income residents of Marion County, Indiana.

TABLE 4

Variables associated with conducting liver specific evaluation (viral serologies, abdominal imaging or GI consultation) in patients with elevated aminotransferases: Multiple Logistic Regression Analyses

Viral Serologies		Abdominal Imaging		GI clinic	
	OR (95% CI)		**OR (95% CI)**		**OR (95% CI)**
Modified Charlson Index		**Ethnicity**		**Insurance**	
0 vs. ≥ 4	1.04 (0.8-1.3)	AA vs. Cau	1.23 (1.1-1.4)	Government vs. Uninsured	1.45 (1.3-1.7)
1 vs. ≥ 4	0.83 (0.7-1.0)			Private vs. Uninsured	0.63 (0.4-0.9)
2-3 vs. ≥ 4	0.78 (0.6-1.0)	**Gender**			
		Female vs. Male	1.38 (1.2-1.6)	**Age**	
Age				1st Quartile vs. 4th	2.1 (1.7-2.6)
1st Quartile vs. 4th	2.2 (1.9-2.5)	**Modified Charlson Index**		2nd vs. 4th	4.3 (3.5-5.3)
2nd vs. 4th	1.8 (1.6-2.1)	0 vs. ≥ 4	0.44 (0.4-0.5)	3rd vs. 4th	3.2 (2.6-3.9)
3rd vs. 4th	1.4 (1.2-1.7)	1 vs. ≥ 4	0.46 (0.4-0.6)		
		2-3 vs. ≥ 4	0.54 (0.4-0.7)	**Modified Charlson Index**	
				0 vs. ≥ 4	0.64 (0.5-0.8)
				1 vs. ≥ 4	0.56 (0.4-0.7)
				2-3 vs. ≥ 4	0.56 (0.4-0.8)
				Weight	
				1st Quartile vs. 4th	1.7 (1.4-2.0)
				2nd vs. 4th	1.8 (1.45-2.1)
				3rd vs. 4th	1.4 (1.15-1.71)