

may even be harmful, while increasing overall medical expenditure.

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### Fasting and Medical Issues During Ramadan

**To the Editor:** There are estimated to be between 1 million and 3 million Muslims living in the United States,<sup>1</sup> and most will participate in ritual daily fasting during the holy month of Ramadan, which in 2005 starts on October 3 and ends on November 2. During Ramadan, Muslims abstain from food and drink from sunrise to sundown, for approximately 13 hours. The fast is broken after the sun sets, with a meal called *iftar*. Children and individuals whose health may be harmed by fasting are exempt from fasting, according to the Qur'an. In addition, Muslims unable to fast during Ramadan may fast at other times of the year to compensate. Physicians should be aware of Ramadan and determine fasting practices among their Muslim patients to detect potential complications arising from this practice.

Serious complications of fasting from Ramadan have not been well documented in the literature, but the most frequently reported is increased risk of hypoglycemia and hyperglycemia in patients with diabetes.<sup>2</sup> Patients with type 2 diabetes may safely fast with close monitoring of blood glucose levels and possible adjustment of medication to avoid hypoglycemia.<sup>3</sup> Oral hypoglycemic agents should be taken in the evening after breaking fast, not in the morning. The *iftar* may be quite large, so that some Muslims report weight gain; we have not noted weight loss during Ramadan. We recently discovered that one diabetic patient in our practice was fasting on Mondays and Thursdays throughout the year to compensate for missed Ramadan fasting in her youth, without adjusting her schedule of medications, resulting in wide variation in her blood glucose levels. Patients with stable

type 1 diabetes have been shown to fast safely, but insulin regimens should be altered to reflect eating times, with long-acting basal insulin taken in the evening and shorter-acting insulin taken before meals.<sup>4,5</sup>

Patients' drug regimens should be examined with particular attention to timing of doses, to ensure adherence during the fast and to avoid complications. In our practice, 1 patient with human immunodeficiency virus (HIV) stopped taking his midday HIV medications during Ramadan, increasing his risk of developing resistance. With diminished fluid intake, diuretics may also pose a risk, particularly in unseasonably hot weather.

Certain groups of patients may need to be advised against fasting, including those with poorly controlled or brittle diabetes and pregnant women. Muslim patients in our practice occasionally choose to fast despite recommendations to the contrary. For those at highest risk, we have requested assistance from Muslim clergy in discussing fasting practices. Some religious scholars do allow intravenous or intramuscular medications, and this strategy can be considered in discussion with clergy.

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### RESEARCH LETTER

#### Nonalcoholic Fatty Liver and Insulin Resistance Among Petrochemical Workers

**To the Editor:** Insulin resistance (IR) and features of the metabolic syndrome are often associated with nonalcoholic fatty liver disease (NAFLD). Insulin resistance has been considered to be essential for the development of NAFLD.<sup>1</sup> However, multiple mechanisms are involved in the pathogenesis of NAFLD.<sup>2</sup> We previously described a form of NAFLD among petrochemical workers, affecting predominantly younger men, causing mild fibrosis and cholesta-

sis.<sup>3,4</sup> In the current study we evaluated the relationship of IR to NAFLD among petrochemical workers.

**Methods.** Forty petrochemical workers with the diagnosis of NAFLD who presented with abnormal alanine aminotransferase, aspartate aminotransferase, and  $\gamma$ -glutamyltransferase levels on 3 or more determinations, were referred to the Hepatology Clinic, Federal University of Bahia, Brazil, between March 2001 and November 2003. All had a history of occupational exposure to chemicals (benzene, xylene, ethylene, dimethylformamide, vinyl chloride, and others) for at least 5 years. Patients, corroborated by family members, indicated the absence of significant ethanol consumption ( $>20$  g/d). Those with use of other drugs and presence of hepatitis B and C virus, hemochromatosis, and autoimmune diseases were excluded. The Ethics Committee for Medical Research at Federal University of Bahia, Brazil, approved the study. All patients provided written informed consent.

Insulin resistance was determined by the homeostasis model assessment (HOMA) index<sup>5</sup> (Method Immunolite 2000 DPC, Los Angeles, Calif). Control HOMA-IR values were obtained from 63 healthy volunteers. Insulin resistance was considered to be present when the HOMA index value was 3 or higher. The cut-off point was validated against the results of the quantitative insulin sensitivity check index (QUICKI).<sup>6</sup> The fifth percentile (value  $<0.337$ ) was used as the QUICKI cut-off point for IR. The concordance between HOMA and QUICKI classifications of IR was 100%.

The following definitions were used: obesity, body mass index greater than 30, and overweight as body mass index (calculated as weight in kilograms divided by the square of height in meters) between 25.0 and 29.9; central obesity, waist circumference greater than 102 cm (men) or greater than 88 cm (women); diabetes mellitus, fasting plasma glucose level of at least 126 mg/dL (6.99 mmol/L) on 2 separate occasions; hyperlipidemia, serum total cholesterol greater than 200 mg/dL (5.18 mmol/L), or high-density lipoprotein cholesterol concentration less than 40 mg/dL (1.03 mmol/L) in men and less than 50 mg/dL (1.29 mmol/L) in women, or low-density cholesterol greater than 130 mg/dL (3.36 mmol/L), or serum triglyceride greater than 150 mg/dL (1.69 mmol/L).

**Results.** Insulin resistance was absent in 29 (72.5%) of the patients with NAFLD (TABLE 1). Among the 11 patients (27.5%) with IR, all had hyperlipidemia, while 54.5% were obese, 72.7% were overweight, and 45.4% had diabetes. Among 29 patients without IR, 34.5% had hyperlipidemia and 27.6% were also overweight, but without central obesity. Hyperlipidemia, obesity, overweight, or diabetes were not observed in 11 (37.9%) of the patients.

Liver biopsy was performed on 32 (80%) of the patients (TABLE 2). Steatohepatitis with fibrosis was detected in 22 (68.8%) of these patients; 17 of these 22 patients (77.3%) did not have IR. All 5 patients with IR had steatohepatitis with fibrosis.

**Comment.** To our knowledge, this is the first study to evaluate IR in patients with NAFLD related to chemical exposure.

**Table 1.** Risk Factors for Nonalcoholic Fatty Liver Disease Among 40 Petrochemical Workers According to the Presence or Absence of Insulin Resistance (IR)

Risk Factor	No. (%)	
	Patients Without IR (HOMA Index Value $<3$ ) (n = 29)	Patients With IR (HOMA Index Value $\geq 3$ ) (n = 11)
Hyperlipidemia	10 (34.5)	11 (100.0)
Obesity + hyperlipidemia	0 (0.0)	6 (54.5)
Overweight + hyperlipidemia	8 (27.6)	8 (72.7)
Diabetes + hyperlipidemia	0 (0.0)	5 (45.4)
No metabolic condition*	11 (37.9)	0 (0.0)

Abbreviation: HOMA, homeostasis model assessment.

\*Hyperlipidemia, obesity, overweight, or diabetes.

**Table 2.** Histological Findings in 32 Petrochemical Workers With Nonalcoholic Fatty Liver Disease

Histological Findings*	Patients Without Insulin Resistance, No. (n = 27)	Patients With Insulin Resistance, No. (n = 5)	Total No. (%)
	Steatosis alone (grade 1)	4	
Steatohepatitis without fibrosis (grade 3)	6	0	6 (18.8)
Steatohepatitis with fibrosis (grade 4)	17	5	22 (68.8)
Fibrosis grade 1	14	3	17 (77.3)
Fibrosis grade 2	3	2	5 (22.7)

\*According to the classification by Matteoni et al.<sup>7</sup>

The majority of patients (72.5%) did not have evidence of IR. In addition, 37.9% of these patients without IR were free of metabolic risk factors. These results indicate that, contrary to prior assumptions,<sup>1</sup> the development of fatty liver is not invariably associated with IR, and other mechanisms may be involved. Potential sources of oxidant stress include mitochondrial injury, cytochrome P450 system induction, and peroxisomal  $\beta$ -oxidation.<sup>2</sup> Such factors may also be relevant to NAFLD/nonalcoholic steatohepatitis (NASH) cases related to exposure to chemicals without IR. The absence of demonstrable IR may explain that this type of NAFLD/NASH, usually asymptomatic, presents with mild histological findings that usually improve after workers are removed from exposure.<sup>3</sup> These findings suggest that the usual recommended measures for treating metabolic syndrome (diet and exercise, for example) may have only limited efficacy in petrochemical-related NAFLD. However, the natural history of this form of NAFLD and its relationship with co-existing metabolic syndrome deserves further investigation.

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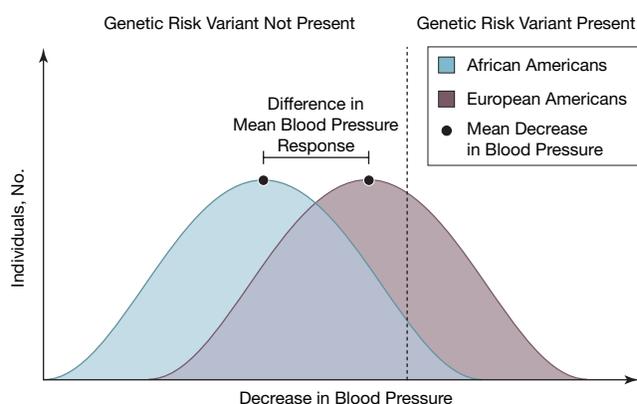
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## CORRECTION

**Incorrect Figure:** In the Special Communication entitled "Genetic Influences on Health: Does Race Matter?" published in the August 24/31, 2005, issue of *JAMA* (2005;294:937-946), there is an error in **FIGURE 1**. The colors for the distributions below the curve were reversed; the key to the Figure is correct. The correct Figure 1 appears below.

**Figure 1.** Hypothetical Relationship Between Genetic Risk, Ancestry, and Race



Distributions of the reduction in blood pressure observed in African Americans and European Americans after treatment with an angiotensin-converting enzyme (ACE) inhibitor. One hypothetical explanation for the mean difference in treatment response is that a genetic risk variant predictive of a positive response to treatment is more common in European Americans (individuals to the right of the dotted line) than in African Americans. Note, however, that some African Americans also have the genetic risk variant and that many African Americans and European Americans who do not have the genetic risk variant have a similar response to treatment (ie, overlap between distributions). In this case, race might not be considered a good predictor of genetic risk or response to treatment. Based on an original concept by Seghal.<sup>9</sup>