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Ethnic Differences in the Effects of Hepatic Fat Deposition on Insulin Resistance in Non-Obese Middle School Girls

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Abstract

Objective—In non-obese youth, to investigate whether hepatic fat deposition and its metabolic consequences vary between ethnic groups.

Design Methods—Thirty-two non-obese girls (12 Hispanic White [H] and 20 non-Hispanic White [NHW] girls), aged 11–14 years old were recruited. Outcome measures were MRI measured hepatic proton density fat fraction (hepatic PDFF), BMI Z-score, waist circumference, fasting insulin, glucose, adiponectin, sex hormone binding globulin [SHBG], ALT, AST, and triglycerides, and HOMA-IR.

Results—There were no significant differences in mean BMI Z-scores ($p=0.546$) or hepatic PDFF ($p=0.275$) between H and NHW girls; however, H girls showed significant correlations between hepatic PDFF and markers of IR (fasting insulin, HOMA-IR, adiponectin, SHBG, triglycerides; all $p<0.05$), while NHW girls showed no significant correlations. Matched by hepatic PDFF or BMI-Z score, H girls had more evidence of IR for a given hepatic PDFF (mean insulin, HOMA-IR, and SHBG; all $p<0.05$) or BMI-Z score (mean insulin and HOMA-IR; all $p<0.01$) than NHW girls.

Conclusions—In non-obese female youth, ethnicity-related differences in effects of hepatic fat on IR are evident, so that in H girls, a given amount of hepatic fat appears to result in a more predictable and greater degree of IR than in NHW girls.

Key Terms

Ethnicity; Non-obese; Insulin Resistance; Hepatic Steatosis

Introduction

In obese individuals, ethnicity and race influence fat distribution that, in turn, influences development of insulin resistance (IR), inflammation, type 2 diabetes mellitus (T2DM) and dyslipidemia. Variations in fat distribution (e.g., subcutaneous versus visceral) are not

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accurately and quantitatively characterized by BMI or DEXA scans [1], but MRI can quantify and locate adiposity to specific anatomic areas. Such variations in the relationship of body mass index (BMI) to measured body fat percentage (BF%) are very important, since adults with normal BMI but higher BF% are still at high risk for dyslipidemia, IR, and inflammation [2], and even T2DM [3]. National Health and Nutrition Examination Survey (NHANES) data indicate that rates of overweight and obesity [4], and relationship of BMI to BF% by DEXA vary with ethnicity and race in adolescents [5]. However, the degree to which fat deposition and its metabolic consequences differ between ethnic and racial groups during early fat accumulation in *non-obese* children and adolescents is not known.

The concept of adipocyte expandability asserts that deposition of fat into small subcutaneous adipocytes rather than “ectopic” sites (visceral adipose tissue, liver, intra-myocellular fat) results in minimal metabolic consequences [6]. In obese adolescents examined by MRI, this idea is supported by the association of *decreased* IR with a predominance of fat deposition in subcutaneous adipose tissue (SCAT) rather than ectopic sites [7]. However, a chronic excessive fat burden can lead to SCAT adipocyte hypertrophy, attraction of pro-inflammatory macrophages, IR, and ectopic fat storage [8]. Visceral adipose tissue (VAT) contains more macrophages than SCAT, more actively produces pro-inflammatory cytokines [9], and was thought by many to be a primary determinant of hepatic and systemic IR [8]. Recent evidence, however, suggests IR is associated with hepatic fat deposition and non-alcoholic fatty liver disease (NAFLD), independent of VAT fat deposition [10, 11].

In both obese and non-obese pre-pubertal children, the ectopic storage of fat in VAT, skeletal muscle, and the liver has been associated with higher IR [12]. With regard to a role of race and ethnicity, MRI images in obese adolescents demonstrate higher levels VAT and hepatic proton-density fat-fraction (hepatic PDFF) in Hispanic (H) and non-Hispanic White (NHW) compared to African Americans, despite overall higher body fat percentages in African Americans [10]. These findings suggest that metabolically deleterious fat patterns are detectable in obese adolescents and are at least partially dependent on genetic background. This study is distinctive in investigating whether, in non-obese children, hepatic fat distribution and its effects on IR already varies by ethnicity.

Methods

Study Population

Female students who attended a local middle school fall registration were invited to participate in this cross-sectional study. Once written consent and assent were obtained, personal and family medical history, and self-identified race and ethnicity (per NIH race and ethnicity criteria for subjects in clinical research) were collected at registration. Individuals of African and Asian descent were not included. Height was measured using a stadiometer and recorded to the nearest 0.5 cm. Waist circumference was measured twice and recorded to the nearest 1mm just above the iliac crests with Graham-Field®; cloth woven measuring tape. Weight was measured without shoes in light clothes on a beam balance platform scale to the nearest 0.1 kg. BMI was then calculated. Self-assessment of Tanner staging for breast and pubic hair was performed [13]. Study entrance criteria included a non-obese BMI percentile of < 90th percentile per CDC 2000 sex- and age-specific BMI growth charts and age 11–14 years old. Based on family self-identification, subjects were allocated to Hispanic White (H) or non-Hispanic White (NHW) groups. To ensure recruitment of a non-obese study group, we set the upper limit for BMI at the 90th percentile, rather than 95th. Exclusion criteria were BMI greater than the 90th percentile for age and gender, Type 1 or Type 2 diabetes mellitus, chronic diseases (including infectious or inflammatory diseases), treatment with glucose metabolism altering (e.g. metformin) or lipid altering (e.g. statin) agents, or pregnancy.

Laboratory

Venipuncture was performed in the early morning after an overnight fast. Blood was processed immediately and analyzed at the University of Wisconsin Hospital and Clinics Laboratory for glucose, insulin, LH, estradiol, AST, ALT, total cholesterol, triglycerides, HDL, sex hormone binding globulin (SHBG), hsCRP (highly sensitive CRP), and free testosterone. Glucose was determined by hexokinase method; insulin, LH, by chemiluminescent immunoassay; AST and ALT by NADH with Pyridoxal-5 phosphate assay, total cholesterol and triglycerides by enzymatic assay; and HDL with direct homogeneous measures (University of Wisconsin Hospital and Clinics Laboratory, Madison, WI). SHBG was measured by a quantitative electrochemiluminescent immunoassay (ARUP Laboratories, Salt Lake City, UT), hsCRP by nephelometric method on the Dimension Vista[®] System (Siemens Healthcare, Munich, Germany), and free testosterone by a quantitative high performance liquid chromatography tandem mass spectrometry-electrochemiluminescent immunoassay (ARUP Laboratories, Salt Lake City, UT). A portion of the sample was analyzed at the University of Wisconsin National Primate Research Center for TNF α and IL-6 by electroimmunoassay (R&D systems, Minneapolis, MN), and adiponectin by radioimmunoassay (Linco-Millipore, St. Charles, MO). Homeostasis model of assessment-insulin resistance (HOMA-IR) was calculated from fasting glucose (mg/dL) and insulin (μ U/ml) values: (fasting glucose $\times$ fasting insulin/405).

Quantitative magnetic resonance imaging was performed at the Wisconsin Institute for Medical Research (WIMR). The Human Subjects Committee of the University of Wisconsin approved all procedures.

Image Acquisition and Reconstruction

Magnetic resonance imaging was performed from liver dome to pelvic floor using a clinical 3T scanner (MR750, GE Healthcare, Waukesha, WI) with a 32-channel phased array body coil (Neocoil, Pewaukee WI). Hepatic PDFF was determined using an investigational version of a chemical shift based water-fat separation method (3D-IDEAL-SPGR) [14, 15]. Separated water-only and fat-only images, as well as hepatic PDFF maps [16] were provided using an on-line reconstruction algorithm method that includes spectral modeling of fat [17], corrects for eddy currents [18], T1 bias [19], T2* decay [20], and noise related bias [19]. Because all known confounders have been addressed, the resulting PDFF map provides an accurate and fundamental measure of the fat concentration in tissue [15, 21].

Hepatic PDFF was determined by averaging PDFF value measured from 9 regions of interest placed in the 9 Couinaud segments of the liver [14, 22]. Hepatic steatosis was defined as a hepatic PDFF >5.56 [23].

Statistics

Fat distribution measures, insulin resistance, and inflammatory markers were summarized in terms of means $\pm$ standard deviations, stratified by group. The comparison of study participant's characteristics between H and NHW was conducted using a two-sample t-test and Fisher's exact test. Nonparametric Spearman's rank correlation analysis was conducted to evaluate the associations between fat distribution measures, insulin resistance and inflammatory markers. Fisher's z-transformation was used to construct 95% confidence intervals (CI) of the correlation coefficients. The study was powered to detect anticipated effect sizes ranging from 1.5–2.2% of hepatic PDFF. Specifically, a target sample size of twenty subjects per ethnicity group provided $>90\%$ power to detect an hepatic PDFF effect size of 1.5% between ethnicity groups at the two-sided 0.05 significance level. Furthermore, in order to evaluate whether the association between fat distribution measures and insulin resistance and inflammatory makers vary by ethnicity, linear regression analysis was

conducted where the interaction term between ethnicity and the fat distribution measures were included as covariates. In order to further evaluate whether a given BMI Z-score or hepatic PDFF had ethnicity-related effects on insulin resistance and inflammation, matched paired comparisons between H and NHW were performed using a paired t-test. Matched pairs according to BMI Z-score and hepatic PDFF were constructed using a greedy matching algorithm [24]. Statistical analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC). All *P* values were 2-sided, and *P* < 0.05 was used to indicate statistical significance.

Results

Characteristics of 32 subjects (12 H, 20 NHW) are presented in Table 1. Between the two groups there were no statistically significant differences in mean age, mean BMI Z-score (BMI Z-score range for H group −0.91 to 1.27 and for NHW group −1.05 to 1.19), mean waist circumference, or occurrence of menarche. The mean BMI Z-scores were consistent with mean BMI percentiles at the 65th percentile in H subjects and the 57th percentile in NHW subjects.

The H subjects had significantly higher mean fasting insulin (22.0 ± 11.9 μ IU/mL vs. 13.7 ± 5.7 μ IU/mL, *p*=0.013), higher mean HOMA-IR (5.0 ± 3.4 vs. 3.0 ± 1.4 , *p*=0.017), and lower mean SHBG (47.3 ± 26.2 nmol/L vs. 73.6 ± 29.8 nmol/L vs. *p*=0.019) than NH subjects. There were no significant differences between H and NHW groups in hepatic PDFF (*p*=0.600), adiponectin (*p*=0.425), hsCRP (*p*=0.211), TNF α (*p*=0.800), free testosterone (*p*=0.471), and all other lab values (data not shown). With the achieved sample size of twelve H subjects and twenty non-Hispanic subjects, a hepatic PDFF effect size of 1.5% was detected with 95% power at the two-sided 0.05 significance level.

Relationship between hepatic PDFF and markers of IR varies with ethnicity

Hispanic subjects had significant correlations between hepatic PDFF and indicators of increasing IR, i.e. strong positive correlations were observed between hepatic PDFF levels and fasting insulin, HOMA-IR, and triglycerides; strong negative correlations were observed between hepatic PDFF levels and SHBG [25, 26] and adiponectin [27] (Table 2 and Figure 1). NHW subjects, on the other hand, had no significant correlations between hepatic PDFF and markers of IR (Table 2 and Figure 1). Comparison of various correlation coefficients with hepatic PDFF revealed significant differences between H and NHW groups (fasting insulin: *r*=0.75 vs. −0.17, *p*=0.005, HOMA-IR: *r*=0.78 vs. −0.20, *p*=0.002, adiponectin: *r*=−0.80 vs. −0.20, *p*=0.030, and SHBG: *r*=−0.81 vs. −0.26, *p*=0.037 (Table 2). Furthermore, a significant interaction between hepatic PDFF and ethnicity was observed in the linear regression model of fasting insulin on hepatic PDFF and ethnicity (*p*=0.007), and HOMA-IR on hepatic PDFF and ethnicity (*p*=0.002). Additionally, a linear model was used to evaluate the association between mean liver fat and SHBG on HOMA-IR and fasting insulin, and significant negative correlations of SHBG with HOMA-IR and insulin resistance were seen in the H group but not the NHW group.

Associations were evaluated using nonparametric Spearman's rank correlation analysis, which is insensitive to outliers. However, given one H subject had much greater hepatic PDFF than any other subject (as demonstrated in Fig 1), analysis excluding that apparent outlier did not change the correlations of hepatic PDFF with markers of IR (data not shown). Also, to account for the effect of puberty on insulin resistance, a comparison of the correlation coefficients of post-menarchal H and NHW subjects' hepatic PDFF with markers of insulin resistance was performed with significant differences between the two ethnic groups remaining for the correlations of hepatic PDFF with HOMA-IR, triglycerides, and SHBG. ALT (Table 2) and AST did not correlate with hepatic PDFF in either group. Three

H children met hepatic PDFF criteria for the diagnosis of NAFLD (i.e. > 5.56% as pictured in Figure 1) [23]. There were no significant correlations of hepatic PDFF with inflammation in either group (data not shown).

When matched for BMI Z-score or hepatic PDFF, IR varies by ethnicity

In order to further evaluate whether a given BMI Z-score or hepatic PDFF had ethnicity-related effects on IR, a subgroup analysis of 12 subjects from both the H and NHW groups were matched for BMI Z-score or hepatic PDFF. When matched by BMI Z-score, the H subjects had statistically significant higher mean fasting insulin ($22.0 \pm 11.9 \mu\text{IU/mL}$ vs. $13.6 \pm 5.7 \mu\text{IU/mL}$, $p=0.01$) and HOMA-IR (5.0 ± 3.39 vs. 3.01 ± 1.2 , $p=0.03$) with a lower SHBG ($47.3 \pm 26.2 \text{ nmol/L}$ vs. $73.6 \pm 29.8 \text{ nmol/L}$, $p=0.009$) than NHW subjects. Similarly, when matched by hepatic PDFF, the H subjects had significantly higher mean fasting insulin ($22.0 \pm 11.9 \mu\text{IU/mL}$ vs. $11.4 \pm 2.8 \mu\text{IU/mL}$, $p=0.001$) and HOMA-IR values (5.0 ± 3.4 vs. 2.5 ± 0.6 , $p=0.002$) than NHW subjects, and a trend towards lower SHBG ($47.3 \pm 26.3 \text{ nmol/L}$ vs. $71.3 \pm 28.8 \text{ nmol/L}$, $p=0.064$).

Discussion

This study provides new knowledge regarding ethnic differences in the relationship between hepatic fat deposition and markers of IR in children and adolescents who are non-obese. Hispanic subjects showed strong correlations between markers of IR and hepatic PDFF, while among non-Hispanic White subjects, these correlations were notably absent. Relationships between hepatic PDFF to markers of IR in non-obese Hispanic subjects were present even though hepatic PDFF quantity did not differ between the two ethnic groups. Also, for a given hepatic PDFF or BMI Z-score there was more associated evidence of IR in the non-obese Hispanic than non-Hispanic white girls. These data indicate that, even in a non-obese state, there are important ethnicity-related differences in the metabolic consequences of fat distribution.

In obese subjects, hepatic fat deposition, rather than visceral adipose tissue volume, has been found to be predictive of systemic IR and dyslipidemia [10, 28]. This study supports and extends the concept of hepatic fat playing an important role in the development of IR to younger and non-obese subjects. Hepatic steatosis is associated with genetic predisposing factors, such as the single nucleotide polymorphism (SNP) of PNLPA3 (patatin-like phospholipase domain-containing protein 3), which is more prevalent in Hispanic individuals [29]. However, in obese adolescents with the PNLPA3 SNP, increases in hepatic fat deposition have not correlated with increasing markers of IR [29, 30].

The results in this study also confirm prior findings that ALT is a poor predictor for hepatic fat deposition and NAFLD, especially in the earliest stages of NAFLD [31]. However, adult data reveal that SHBG, independent of visceral adiposity, is predictive of hepatic fat deposition [26]. SHBG is produced by hepatocytes and, unlike ALT, has age, gender, and pubertal reference ranges. In the Hispanic girls studied here, a strong correlation of hepatic PDFF with SHBG suggests that SHBG could be an alternative marker for pediatric NAFLD risk stratification. As SHBG values have been found to vary with ethnicity and race in children and adults, race or ethnicity based SHBG reference ranges may increase the diagnostic utility of SHBG. [32, 33]. Additionally, SHBG has been found to be lower in children at greater risk for metabolic syndrome [34] and in woman with polycystic ovarian syndrome, groups who also have an increased risk for NAFLD [35]. Thus, in certain children at higher risk for NAFLD development and metabolic syndrome, SHBG may function as a useful screen prior to the development of obesity [36].

Strengths of this study include a focus on non-obese adolescents and the use of site-specific MRI measurement of hepatic fat deposition obtained in conjunction with laboratory assessments. A potential limitation of our study is use of Hispanic as a broad ethnic group, which likely includes genetic and cultural heterogeneity among Hispanic subjects. Enrollment was relatively small and allowed analysis of only two groups, H and NHW girls. More extensive family history, including ethnicity and country of origin for grandparents, would more precisely define ethnicity. Further, inclusion of genetic studies, such as PNLPA3, would capture genetic variability that specifically influences fat deposition and risk for metabolic disease [29]. Whether the findings in our study are applicable to male subjects, and adolescents of other races and ethnicities, remains uncertain. With the inclusion criteria of subjects up to the 90th percentile the chance for children approaching an obese state would arise; however, the BMI Z-scores were not significantly different and the mean BMI Z-scores were just below the 65th and 57th percentiles for the H and NHW girls, respectively. Although efforts were made to document pubertal maturation (self-assessment and LH levels), lack of formal physical examinations and variations in pubertal status could remain potential confounding factors, given important effects of puberty on insulin resistance [37]. Additionally, although an oral glucose tolerance test (OGTT) should in principle, correlate more closely with the hyperinsulinemic-euglycemic clamp, fasting indices have been shown to be of value similar to OGTT in assessing IR in obese adolescents [38].

In conclusion, in non-obese girls, there are ethnic differences in correlations of hepatic fat fraction to markers of insulin resistance. Specifically, non-obese Hispanic girls exhibit strong correlations between hepatic fat fraction and IR that are not seen in non-obese non-Hispanic White girls. Further, when matched by hepatic PDFF or BMI z-score, non-obese Hispanic greater levels of insulin resistance than their non-Hispanic White peers, indicating that, even in children with a non-obese BMI, ethnicity-related differences in metabolic risk factors exist. These findings suggest potential value for ethnicity-customized BMI percentile risk thresholds. However, such an approach could be complicated by lower specificity and potential for stigmatization. More importantly, awareness of detrimental effects of early fat deposition demonstrated in this study should strengthen promotion of nutrition and physical activity policies that can reach all children prior to the onset of obesity, and would particularly benefit those with greater risk for health-damaging consequences of caloric excess.

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Abbreviations

H	Hispanic
Hepatic PDFF	hepatic proton density fat fraction
HOMA-IR	homeostatic model assessment of insulin resistance
IR	insulin resistance
NAFLD	non-alcoholic fatty liver disease

NHW	non-Hispanic White
SCAT	subcutaneous adipose tissue
SHBG	sex hormone binding globulin
VAT	visceral adipose tissue

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What is already known about this subject

- In obese youth, the degree of hepatic fat deposition varies with ethnicity and race.
- Hepatic fat deposition, independent of visceral fat deposition, is associated with insulin resistance.

What this study adds

- Non-obese Hispanic girls exhibit strong correlations of hepatic fat fraction with markers of insulin resistance that are absent in non-obese, non-Hispanic White girls.
- Non-obese Hispanic girls demonstrate greater insulin resistance than non-obese, non-Hispanic White girls when matched by hepatic fat fraction.
- Thus, in non-obese girls, ethnicity-related differences in effects of hepatic fat on IR are evident.

Figure 1.

Correlations of hepatic proton density fat fraction (hepatic PDFF) with insulin resistance (IR) in non-obese girls. No correlation was observed between the HFF and IR in non-Hispanic White (NHW) girls. Solid regression line is for Hispanic and dotted regression line is for NHW girls. Hepatic PDFF 5.56% consistent with hepatic steatosis

TABLE 1

Characteristics of study participants

	Hispanic (N=12)		Non-Hispanic White (N=20)		
	Mean ± SD		Mean ± SD		p-value
Mean Age (years)	12.2 ±1.1		12.4 ±1.1		0.712
Mean BMI Z-score	0.38 ±0.72		0.17 ±0.70		0.546
Mean Waist Circumference (cm)	74 ±10		70 ±6.5		0.275
Mean LH (mIU/mL)	7.2±9		4.1±4.5		0.448
Mean Hepatic					
Proton Density Fat Fraction	3.64% ±2.69%		2.48% ±0.83%		0.641
Percent Post-Menarcheal	58% (7/12)		42% (8/20)		0.467

TABLE 2

Correlations of hepatic PDFF with metabolic parameters varies by ethnicity

	Hispanic (H)	Non-Hispanic White (NHW)	
	Correlation coefficient [†] (95% CI)	Correlation coefficient [†] (95% CI)	Comparison of H and NHW Correlation coefficients
Fasting Insulin (μIU/mL)	0.75** (0.27–0.92)	–0.17 (–0.58–0.31)	p=0.005
HOMA-IR	0.78** (0.33–0.93)	–0.20 (–0.59–0.29)	p=0.002
Adiponectin (ng/dL)	–0.80** (–0.94–0.40)	–0.20 (–0.60–0.28)	p=0.030
SHBG (nmol/L)	–0.81** (–0.94–0.41)	–0.26 (–0.63–0.23)	p=0.037
Triglycerides (mg/dL)	0.65* (0.09–0.89)	0.01 (–0.45–0.46)	p=0.063
ALT (U/L)	0.11 (–0.50–0.64)	–0.37 (–0.70–0.12)	p=0.226

* p-value < 0.05;

** p-value < 0.01;

PDFF, proton density fat fraction; SHBG, sex hormone binding globulin; ALT, alanine aminotransferase.

[†] Spearman's rank correlation coefficient.