Published in final edited form as:

J Pediatr Endocrinol Metab. 2016 February 1; 29(2): 153–156. doi:10.1515/jpem-2015-0158.

Use of the triglyceride to HDL cholesterol ratio for assessing insulin sensitivity in overweight and obese children in rural Appalachia

Kristie Grove Bridges*, Traci Jarrett,

Prevention Research Center, School of Public Health, West Virginia University; West Virginia Clinical and Translational Science Institute, Morgantown WV, USA; and Visiting Scholar, University of Kentucky, Lexington, KY, USA

Anthony Thorpe,

Department of Clinical Sciences, West Virginia School of Osteopathic Medicine, Lewisburg WV, USA

Adam Baus, and

Office of Health Services Research, School of Public Health, West Virginia University; West Virginia Clinical and Translational Science Institute, Morgantown, WV, USA

Jill Cochran

Department of Clinical Sciences, West Virginia School of Osteopathic Medicine, Lewisburg WV, USA

Abstract

Background—Studies have suggested that triglyceride to HDL-cholesterol ratio (TRG/HDL) is a surrogate marker of insulin resistance (IR), but information regarding its use in pediatric patients is limited.

Objective—This study investigated the ability of TRG/HDL ratio to assess IR in obese and overweight children.

Subjects—The sample consisted of de-identified electronic medical records of patients aged 10–17 years ($n = 223$).

Materials and methods—Logistic regression was performed using TRG/HDL ratio as a predictor of hyperinsulinemia or IR defined using homeostasis model assessment score.

Results—TRG/HDL ratio had limited ability to predict hyperinsulinemia (AUROC 0.71) or IR (AUROC 0.72). Although females had higher insulin levels, male patients were significantly more likely to have hypertriglyceridemia and impaired fasting glucose.

*Corresponding author: **Kristie Grove Bridges**, Department of Biomedical Sciences, West Virginia School of Osteopathic Medicine, Lewisburg, WV 24901, USA, Phone: 304-647-6223, kbridges@osteo.wvso.edu.

All authors have read the journal's policy on disclosure of potential conflicts of interest and have no conflicts to disclose.

Conclusions—TRG/HDL ratio was not adequate for predicting IR in this population. Gender differences in the development of obesity-related metabolic abnormalities may impact the choice of screening studies in pediatric patients.

Keywords

dyslipidemia; insulin resistance; pediatric obesity

Introduction

Insulin resistance (IR) is believed to be a significant risk factor for early development of type 2 diabetes in obese and overweight children, but there is little agreement on how to effectively screen this population (1). Euglycemic hyperinsulinemic clamp studies are considered to be the gold standard for quantifying insulin sensitivity. However, these studies are highly invasive and cannot be done in most primary care settings. The oral glucose tolerance test (OGTT) is less invasive and time consuming but still requires multiple sampling. Surrogate measures of insulin sensitivity include fasting insulin level, which increases in response to peripheral IR, and formulas based on both fasting insulin and glucose such as the homeostasis model assessment (HOMA) and the quantitative insulin-sensitivity check index (QUICKI) (2). These surrogates have been widely used in adult populations, but studies regarding their correlation with euglycemic hyperinsulinemic clamp or OGTT have been contradictory, and there are no established cutoffs for HOMA or QUICKI in children (2–4). Although these approaches to screening are simpler than performing the OGTT, they are expensive and require venipuncture for which there is a high degree of noncompliance in rural pediatric populations (5). In a group of obese and overweight children referred for fasting glucose and lipid screening at our clinic in rural West Virginia, fewer than half followed through and visited the lab for venipuncture (J. Cochran, J. Fogus, H. Anderson, et al. unpublished data). West Virginia is the only US state that lies completely within the Appalachian Region, an area that follows the Appalachian mountain range from northern Mississippi to southern New York. Several factors including distance and transportation, cost, time, and concerns regarding needles were identified as being significant barriers to participation in cholesterol screening in Appalachian patients (5). The development of more convenient and cost-effective screening tools would facilitate the identification of children at the greatest risk of developing diabetes or cardiovascular disease.

Triglyceride (TRG) metabolism is regulated in part by insulin and hypertriglyceridemia is commonly seen in patients with diabetes or IR (6). IR is also associated with low levels of HDL cholesterol (HDL-C), and several studies have suggested that TRG/HDL ratio may be a useful indicator of insulin sensitivity in adults (7–9). In children and young adults, TRG/HDL ratio was shown to be associated with both QUICKI and HOMA as well as with arterial thickness (10, 11). In addition, a study in obese children suggested that a TRG/HDL ratio greater than 2.27 was a significant cut point for predicting IR in Caucasians but not in Hispanics or African Americans (12). The goal of this study was to determine if TRG/HDL ratio could be used to assess insulin sensitivity in a population of overweight and obese patients in rural Appalachia. Because a lipid panel can be performed point-of-care using

finger stick capillary blood sampling, this could provide a more convenient approach to identifying patients with insulin resistance particularly in rural areas.

Materials and methods

This project was reviewed by the West Virginia School of Osteopathic Medicine Institutional Review Board and complies with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. De-identified data were obtained from pediatric electronic medical records available at the Robert C. Byrd Clinic in Lewisburg, WV, USA. All obese and overweight patients under the age of 18 who had received fasting insulin, glucose and lipid panel screening in a two-year period (2012–2014) were included in the sample. Data for this study were collected through chart review using a standardized data collection tool. Initial exploratory analyses were completed using Excel (Microsoft Corporation, Redmond, WA, USA), with subsequent analyses completed in SPSS Version 22.0 (IBM, Armonk, NY, USA). The extracted data included patient age; gender; body mass index (BMI) percentile; geographic location using the first three digits of the zip code; and results of fasting insulin, glucose, and lipid testing. Additional data extracted from the medical record included hypertension diagnoses made by the child's provider. This clinic uses the Centers for Disease Control guidelines for diagnosis of hypertension which requires systolic or diastolic blood pressure above the 95th percentile that persists over three separate visits (13).

Children with a BMI at or above the 85th percentile and lower than the 95th percentile for their age and sex were classified as being overweight. Children with a BMI at or above the 95th percentile were classified as being obese (14). HOMA was defined as (fasting insulin [μ IU/mL] x fasting glucose [mg/dL])/405 (15). Hyperinsulinemia was defined as a fasting insulin level $> 25 \mu$ IU/mL and impaired fasting glucose was defined as a fasting blood glucose level between 100 and 125 mg/dL, cutoffs recommended in the American Diabetes Association Standards of Medical Care in Diabetes (16). It has been shown that HOMA is no better than fasting insulin at predicting euglycemic hyperinsulinemic clamp results in children and there are no accepted cutoffs for HOMA in pediatric patient (1, 15). Therefore, we compared the ability of TRG/HDL ratio to predict IR using two different definitions of IR used previously in pediatric studies – hyperinsulinemia (insulin $> 25 \mu$ IU/mL) and the top quartile of HOMA for the population (8, 17). Cutoffs recommended in the Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents were used to define dyslipidemia (18). Exploratory analysis was performed to examine distribution of continuous variables. Means were compared in male and female patients using the Mann-Whitney U-test as values were not normally distributed. The χ^2 -test was used to compare categorical variables. Spearman's rho was used to investigate correlations between continuous variables. Binary logistic regression was performed to investigate the ability of TRG/HDL ratio to predict the presence of hyperinsulinemia or IR defined as the top quartile of HOMA. Control variables in each model included gender, age, and BMI percentile. Each model was assessed for model fit and postestimate sensitivity and specificity analysis (cutoff 0.5), and receiver operator curves were conducted.

Results

Data were available for 223 patients (124 female and 99 male). The average age of the population was 13.4 years (range, 10–17). Seventy nine percent of the patients were obese, and 11% had a diagnosis of hypertension. Hyperinsulinemia was seen in 27% of the patients whereas 49% had a TRG/HDL ratio over 2.27, a cutoff previously suggested to be predictive of IR in Caucasian patients. A comparison of laboratory values in male and female patients is shown in Table 1. While female patients had significantly higher fasting insulin levels, male patients had higher fasting blood glucose, lower HDL-C, and higher TRG/HDL ratio. As shown in Table 2, male patients were more likely than female patients to have impaired fasting glucose, hypertriglyceridemia or low levels of HDL-C.

TRG/HDL ratio correlated significantly with BMI percentile ($r = 0.192$, $p = 0.004$); insulin levels ($r = 0.358$, $p < 0.001$); and HOMA ($r = 0.376$, $p < 0.001$). There was no correlation between any of the metabolic parameters and age. The results of the regression models indicated that, although TRG/HDL ratio significantly predicted hyperinsulinemia (OR = 1.42, CI 1.18–1.70) and IR as defined by the top quartile of HOMA (OR = 1.47, CI 1.22–1.79), the postestimation indicated only adequate prediction of the outcome variables (Table 3). Model fit was improved when TRG/HDL ratio was added to a null model which contained the control variables of age, gender and BMI percentile. Likelihood ratio χ^2 of the null model was 14.32 ($p = 0.003$) for hyperinsulinemia and 6.98 ($p = 0.073$) for top quartile of HOMA. Addition of TRG/HDL ratio improved these values to 30.37 ($p < 0.001$) and 30.36 ($p < 0.001$), respectively.

Discussion

In this study of obese and overweight Appalachian children, there was a significant correlation between TRG/HDL ratio and both insulin levels and HOMA. These results are similar to those seen in a group of 234 patients participating in the Wausau School Project (10). However, TRG/HDL ratio was not found to be a useful predictor of IR in our patients. These findings differ from those of another study which proposed 2.27 as a cutoff TRG/HDL ratio for predicting IR in obese Caucasian patients (12). That study did not report a significant sex difference in TRG/HDL ratio. However, in our population, male patients were more likely to have hypertriglyceridemia and low levels of HDL-C and had significantly higher TRG/HDL ratio than female patients. Another interesting sex difference seen in our population was the increased prevalence of impaired fasting glucose in male patients. While insulin levels were higher overall in females, the male patients were more likely to have metabolic abnormalities associated with IR including hypertriglyceridemia (33.3% vs. 18.5%) and impaired fasting glucose (22.2% vs. 8.9%). These results are similar to those reported by Tester et al. in a study of pediatric patients in Northern California (19). In this population of predominantly Hispanic obese and overweight children, male patients were more likely to have impaired fasting glucose while female patients were more likely to have elevated HOMA.

The effects of pubertal changes on glucose metabolism and insulin sensitivity are not well understood but it has been shown that HOMA increases during puberty (3, 20). Our study is

limited by the fact that Tanner staging data were not available, and we could not investigate the impact of puberty on metabolic abnormalities in this population. There was no significant difference in average age of the male and female patients, but a larger percentage of the girls would presumably have entered puberty (21). This could potentially explain the higher average insulin levels seen in the female patients. However, the prevalence of hyperinsulinemia was similar in the two sexes, and it is unclear why the male patients in our study were more likely to have impaired fasting glucose. Longitudinal studies using the tolbutamide-modified frequently sampled intravenous glucose tolerance test to investigate insulin sensitivity and beta-cell function during adolescence have shown that puberty is associated with a significant decrease in insulin sensitivity and a lower than expected compensatory increase in insulin secretion (22, 23). However, these studies were too small to investigate sex differences, and it is not known if female adolescents may have more effective pancreatic compensation for peripheral IR than males. Some screening guidelines recommend the measurement of fasting insulin and glucose in obese children while others recommend only fasting glucose (14, 24, 25). In this population, glucose measurement alone resulted in the identification of significantly fewer females with abnormal values than males whereas the prevalence of hyperinsulinemia was similar in both sexes. If a goal of screening is to find early abnormalities that may help motivate patients and their parents to make lifestyle changes, the use of insulin as a screening tool may be more important in female children.

Although our study is limited by the fact that surrogate measures of insulin sensitivity were used instead of euglycemic hyperinsulinemic clamp, the findings suggest that measurement of TRG/HDL ratio is not sufficient for identifying children with metabolic abnormalities associated with obesity. Our findings also suggest that there may be gender differences in the progression of these metabolic disturbances that may impact the ability of screening studies to identify children at the greatest risk. In the study by Tester et al., no gender differences were seen in HbA_{1c} which identified more pre-diabetic patients than fasting glucose measurement (19). Because HbA_{1c} does not require fasting, it may be a better screening tool than TRG/HDL ratio or insulin and glucose based measures. Given the poor compliance in obtaining fasting labs in rural pediatric patients, other means of evaluating IR in this population should be investigated.

Acknowledgments

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under award number U54GM104942. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1

Characteristics of the study population.

	Female (n = 124)	Male (n = 99)	p-Value
Age, years	13.40±2.26	13.39±2.08	0.940
BMI percentile	95.94±6.01	96.20±5.71	0.352
Glucose, mg/dL	90.11±8.90	95.75±8.01	<0.001
HOMA-IR	5.28±3.58	4.94±3.79	0.087
Insulin, μ IU/mL	23.48±15.04	20.63±14.70	0.011
LDL-C, mg/dL	89.50±23.55	89.99±24.51	0.764
HDL-C, mg/dL	44.42±10.44	39.77±7.93	0.001
TRG, mg/dL	101.06±53.16	117.71±72.19	0.111
Total C, mg/dL	154.07±29.59	153.28±28.16	0.935
TRG/HDL ratio	2.50±1.84	3.30±1.90	0.011

Values are means±SD.

Table 2

Percentage of patients with metabolic abnormalities.

	Female (n = 124)	Male (n = 99)	χ^2 (p-Value)
Obese	78.2%	80.8%	0.224 (0.636)
Hypertension	9.7%	13.1%	0.660 (0.417)
Insulin > 25 μ IU/mL	28.2%	26.3%	0.107 (0.744)
IFG	8.9%	22.2%	7.78 (0.005)
Total cholesterol > 200 mg/dL	8.1%	7.1%	0.077 (0.781)
LDL-C > 130 mg/dL	6.5%	5.1%	0.197 (0.657)
TRG > 130 mg/dL	18.5%	33.3%	6.40 (0.011)
HDL-C < 40 mg/dL	33.1%	47.5%	4.79 (0.029)

Table 3

Sensitivity and specificity with which TRG/HDL ratio identifies IR defined as hyperinsulinemia or the top quartile of HOMA.

	Sensitivity, %	Specificity, %	Area under ROC
Hyperinsulinemia	16.4	97.6	0.71
HOMA top quartile	14.8	97.6	0.72