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Low HDL-C is a non-fasting marker of insulin resistance in children

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Abstract

Objectives: Childhood obesity and associated comorbidities, including insulin resistance, are increasing in the United States. Our objectives were to (1) determine the prevalence of insulin resistance in children seen in dyslipidemia clinic and (2) evaluate which aspects of the lipid profile correlate with insulin resistance.

Methods: Children and adolescents seen in a specialized pediatric dyslipidemia clinic without secondary diagnoses known to alter the lipid panel were included. Simultaneous fasting lipid panel, insulin, and glucose levels were available in 572 children (50.5% male).

Results: Mean patient age was 15.0 ± 3.6 years with the majority being over 10 years of age (92.5%). Mean BMI was 29.8 ± 8.1 kg/m^2 and BMI standard deviation score was 1.80 ± 0.9. Mean HOMA-IR was 6.2 ± 5.7 with a range of 0.4–49.3, and interquartile range of 2.7–7.6. Triglyceride level had a positive correlation with HOMA-IR ($p<0.001$). HDL-C negatively correlated with HOMA-IR even controlling for triglyceride level by multivariate analysis ($p=0.001$) and HDL-C <30 mg/dL predicted IR with 41.5% PPV.

Conclusions: In children and adolescents with dyslipidemia, insulin resistance is common and significantly correlates with reduced HDL-C levels. Non-fasting samples are easier to obtain in children and low HDL-C, which is minimally affected on non-fasting samples, could be an easily obtained indicator of IR. Increasing detection of insulin resistance in children with dyslipidemia may provide greater opportunities for lifestyle interventions and possible pharmacotherapy to modify cardiovascular risk.

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Keywords: dyslipidemia; HDL-C; insulin resistance.

Introduction

Obesity is increasing in the US and currently 20% of children age 12–19 years are obese [1, 2]. Screening for diabetes with hemoglobin A1c is recommended at age 10 years or start of puberty for overweight or obese children with additional risk factors for diabetes [3, 4]. Using these criteria, approximately one-quarter of US children and adolescents are eligible for diabetes screening, of which only 4% have elevation of hemoglobin A1c greater than or equal to 5.7% [5]. However, nearly half of obese adolescents have elevation of homeostatic model assessment of insulin resistance (HOMA-IR) indicating insulin resistance (IR), an established risk factor for metabolic syndrome, type 2 diabetes mellitus (T2D), and future cardiovascular disease [6]. Therefore, reliance on hemoglobin A1c leads to under-detection of IR.

The prevalence of T2D has increased by 30.5% among adolescents between 2001 and 2009 [7] and could quadruple by 2050 [8]. Furthermore, T2D in youth responds poorly to metformin, progresses more rapidly to insulin dependence, and demonstrates increased risk for complications at a young age [9]. Detection of IR is a valuable step toward early intervention and prevention of T2D in children and adolescents.

Given the recommendations for universal screening for dyslipidemia in children and adolescents at 9–11 years of age and again at 17–21 years of age, it would be advantageous if lipid panels could also be used as a screening tool for children at risk for IR. We aimed to (1) evaluate the prevalence of IR in pediatric patients followed for dyslipidemia and (2) determine which aspects of the lipid profile correlate with IR.

Materials and methods

Study setting and population

Children seen in pediatric dyslipidemia clinic between 1/1/2010 and 12/11/2020 were studied. Those with simultaneous fasting insulin and glucose measurement prior to medical intervention for dyslipidemia

were included. Exclusion criteria included existing diagnosis of type 1 or type 2 diabetes, chronic renal disease, chronic inflammatory disease, history of transplant, history of childhood cancer, and prior or current use of medication known to alter the lipid panel (including metformin, insulin, statins, atypical antipsychotics, PEG-asparaginase, and isotretinoin). Children with a history of SSRI use were not excluded.

This study was reviewed and approved by the University of Wisconsin Institutional Review Board.

Measures

Demographic data included age, sex, BMI, and BMI standard deviation (SDS). IR was measured by HOMA-IR, which was calculated by the formula HOMA-IR=(fasting glucose in mg/dL*fasting insulin in mIU/L)/405. HOMA-IR of 5.0 or greater was considered indicative of IR based on results from previous population studies in this age group [6]. Data were collected on patients' lipid panels including triglycerides (TG), total cholesterol, high density lipoproteins (HDL-C), non-HDL-C, low-density lipoproteins (LDL-C), and TG/HDL-C ratio. Laboratory reference ranges for the lipid panel are those recommended in the 2011 Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report [10].

Statistical analysis

Descriptive statistics were computed on demographic factors, baseline HOMA-IR levels, and lipid panel. To determine the association between aspects of the lipid panel and HOMA-IR, univariate and multivariate linear regression models were constructed with baseline HOMA-IR as the dependent variable and measures in the lipid panel as predictors.

A p value <0.05 was considered statistically significant. Analyses were performed with the statistical software Stata/SE 16.1 (StataCorp LLC, College Station, TX).

Results

Of the 1,914 patients seen in lipid clinic during the study period, simultaneous fasting lipid panel, insulin, and glucose levels were available for 572 children after applying exclusion criteria (shown in Figure 1). Mean patient age was 15.0 ± 3.6 years. Demographic and baseline laboratory data are shown in Table 1.

All components of the lipid panel had statistically significant association with HOMA-IR as shown in Table 2. Total cholesterol, HDL-C, non-HDL-C, and LDL-C levels were negatively associated with HOMA-IR by linear regression. Positive association was seen with TG level and TG/HDL-C ratio compared to HOMA-IR.

Even after adjustment for TG level, HDL-C remained negatively associated with HOMA-IR level (β=−0.082, 95% CI −0.128 to −0.035) (shown in Figure 2). For predicting elevation of HOMA-IR, a cutoff of HDL-C ≤30 had a sensitivity of 86.0%, specificity of 6.7%, PPV of 41.5%, and NPV of 38.2%.

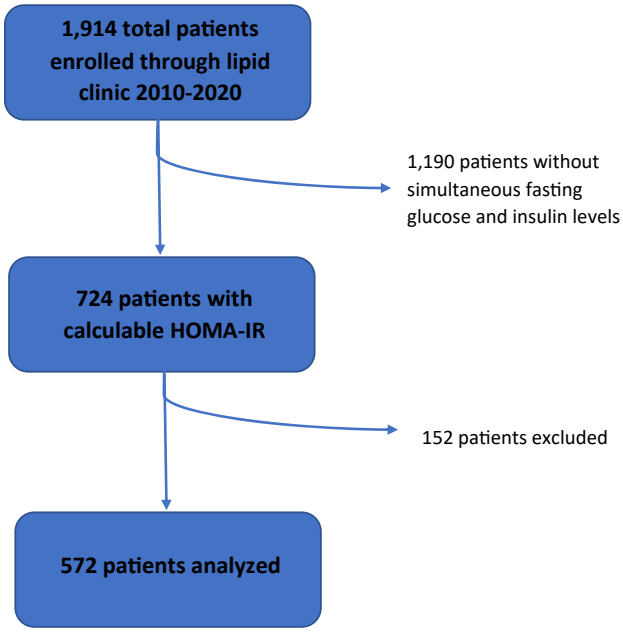

Figure 1: Flowchart indicating process of selection of patients to be analyzed in this study.
Exclusion criteria included those with a medical condition or history of medication use known to alter an aspect of the lipid profile.

Discussion

In the setting of IR, decrease in HDL-C is the consequence of both diminished hepatic and peripheral insulin action, including reduction in lipoprotein lipase activity. While reduction of HDL-C is a common feature of IR in adults, an HDL-C cutoff designating IR has not been established in pediatric patients. Based on HOMA-IR measurement, IR was a common finding in this group of children and adolescents with dyslipidemia. Although there is no HOMA-IR level which is universally agreed to define IR, NHANES data of US adolescents showed a mean HOMA-IR of 2.3 in children of normal weight and 4.9 in obese children [6]. Using a HOMA-IR level greater than or equal to 5.0 to define IR for our population, 43.7% demonstrated IR.

Given that universal screening for dyslipidemia is recommended in children, the lipid panel could provide a valuable opportunity to detect IR, which can be present prior to elevation in hemoglobin A1c or fasting glucose. In this study, HDL-C levels negatively and independently correlated with HOMA-IR. As fasting does not alter HDL-C measurement (contrary to other lipid panel measurements) and fasting samples can be challenging to obtain in

Table 1: Characteristics of patients in pediatric dyslipidemia clinic from 2010 to 2020 who had simultaneous fasting glucose and insulin levels along with a fasting lipid panel (N=572).

Characteristics	Values
Demographics	
Age in years, mean (SD)	15.0 (3.6)
Male, %	50.5
BMI in kg/m^2, mean (SD)	29.8 (8.1)
BMI SDS, mean (SD)	1.80 (0.9)
BMI <85th percentile, n (%)	61 (10.7)
BMI 85th to <95th percentile, n (%)	423 (74.0)
BMI ≥95th percentile, n (%)	17 (3.0)
Not available, n (%)	71 (12.4)
Available race information, n (%)	214 (37.4)
Race in those identifying, n (%)	
White	180 (84.1)
Black or African–American person	14 (6.5)
Asian	9 (4.2)
American Indian or Alaska Native	10 (4.7)
Hawaiian or Pacific Islander	1 (0.5)
Labs at baseline	
HOMA-IR, mean (SD)	6.2 (5.7)
HOMA-IR>5.0, %	43.7
TG in mg/dL, mean (SD)	169.0 (124.4)
HDL-C in mg/dL, mean (SD)	41.3 (10.8)
Non-HDL-C in mg/dL, mean (SD)	142.6 (36.3)
LDL-C in mg/dL, mean (SD)	110.3 (35.2)
Total cholesterol in mg/dL, mean (SD)	183.9 (38.4)
TG/HDL-C ratio, mean (SD)	4.9 (6.9)
Positive/negative predictive value for IR	
HDL-C 30 mg/dL	41.5% PPV; 38.2% NPV

Table 2: Linear regression models examining the association between HOMA-IR and lipid panel components.

Predictor	Univariate analysis β (95% CI)	Multivariate analysis β (95% CI)
TG	0.011 (0.007–0.015)	0.006 (0.001–0.010)
HDL-C	−0.104 (−0.147 to −0.062)	−0.082 (−0.128 to −0.035)
Non-HDL-C	−0.018 (−0.031 to −0.005)	
Total cholesterol	−0.024 (−0.036 to −0.011)	
LDL-C	−0.032 (−0.046 to −0.019)	
TG/HDL-C ratio	0.089 (0.019–0.160)	

children, low HDL-C may serve as a non-fasting marker of IR [11]. It should be taken into account that HDL-C levels are compared to an indirect measure of IR, but studies have found strong correlation between HOMA-IR and hyperinsulinemic–euglycemic clamp which is considered the gold standard for measuring insulin sensitivity [12]. Increased detection of IR could provide opportunities for earlier preventative lifestyle intervention and possible pharmacotherapy to modify diabetes and cardiovascular risk. In adults, metformin can contribute to preventing progression to T2D in those with IR [13]. The few studies of use of metformin in children at risk for T2D have suggested some short-term benefits.

A recent study demonstrated higher HOMA-IR levels in adult statin users, particularly those on hydrophilic statins [14]. In our study population, seven children had available HOMA-IR levels before and after statin initiation (range of time on statin at second HOMA-IR measurement was 0.58–5.42 years). Self-reported adherence was documented; all patients reported good adherence to their statin. There was no indication that statins increased IR in this small cohort. Four of the seven patients had a decrease of more than 1.0 on HOMA-IR level after starting a statin. Only one patient had a notable increase in HOMA-IR after statin initiation, but both HOMA-IR levels denoted a low degree of IR (HOMA-IR change from 0.79 to 2.31). BMI percentile between HOMA-IR levels had not decreased more than 1.0% in any patient. Of note, these seven patients were all prescribed atorvastatin, a lipophilic statin, which may have less impact on insulin sensitivity. Further studies are needed to support our observations and determine if there is greater impact of hydrophilic statins such as rosuvastatin and pravastatin on IR, particularly as adolescence is already a period of heightened IR and a common time for presentation of youth-onset T2D.

Limitations of the study include a focus on children with known dyslipidemia and the majority of study participants were obese, so generalization of the findings to all youth is uncertain. Analysis of the influence of weight status on the correlation between HDL-C and HOMA-IR did not show a significant difference between children of normal weight and those who were overweight/obese (p=0.620 by stratified regression models). Of those with information on race, a significant majority were white, which may limit applicability to other populations. Identification of risk factors for T2D (family history, presence of acanthosis or other conditions associated with IR) was not available for our study population. Application of our use of HDL-C as a screen for IR in those meeting criteria for T2D screening based on their risk factors would be valuable. Additionally, pubertal stage of our participants at the time of determination of HOMA-IR was not assessed. As puberty is a time of increased IR in adolescents, adjustment of HOMA-IR cutoff by stage of puberty may impact the accuracy of HDL-C as a predictive measure of IR.

Strengths of this study include the large sample size, simultaneous measurement of insulin and glucose to

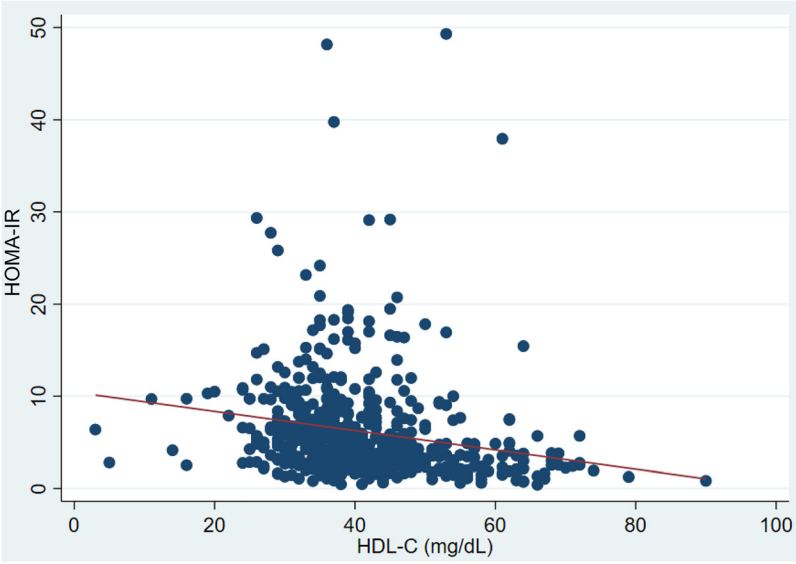

Figure 2: Relationship of HDL-C and HOMA-IR. HDL-C level had a significant negative correlation with HOMA-IR ($p<0.01$) in children with dyslipidemia.

calculate HOMA-IR, and removal of patients who had potential contributing causes of dyslipidemia.

In conclusion, low HDL-C may serve as a non-fasting marker of IR, facilitating screening for this important metabolic health and cardiovascular risk factor. Further studies evaluating the effect of statins on IR in children are needed with larger sample size as well as consideration of the pubertal stage and puberty's influence on insulin sensitivity.

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Author contributions: Conceptualization, design, and construction of the methodology of the project was performed by all authors involved. Formal analysis of the data was performed by Xiao Zhang, with direction from Dr. Zevin. The initial draft of the manuscript was composed by Dr. Zevin. Supervision was provided was Drs. Carrel and Peterson, as well as Ann Dodge. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Stock in Pfizer, Johnson and Johnson, and Merck owned by Ann Dodge MS RN CPNP. No other conflicts identified among other authors.

Informed consent: Not applicable.

Ethical approval: This study protocol was reviewed and approved by the University of Wisconsin Health Sciences Institutional Review Board.

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