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Insulin resistance is not associated with thermogenic effect of a high-fat meal in obese children

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Abstract

In adults, insulin resistance may decrease thermogenic effect of food, contributing to weight gain. We aimed to determine the effect of insulin resistance on energy expenditure in children with long-standing obesity. We hypothesized that thermogenic effect of food would decrease with increasing insulin resistance. Energy expenditure was measured using whole room indirect calorimetry in obese children 7 – 18 years old. Participants were fed a high-fat meal with energy content equal to 35% of measured resting energy expenditure. Thermogenic effect of food was measured for 180 minutes post-test meal and expressed as a percent of calories consumed. Body composition was assessed using whole body dual energy x-ray absorptiometry. Fasting glucose, insulin and hemoglobin A1C were measured. Complete data were available for 25 children (median age 12.1 years old, 52% male). As expected, a significant decrease in resting energy expenditure was observed with increasing Tanner stage ($p=0.02$ by Kruskal-Wallis test). Insulin sensitivity, as determined by homeostasis model assessment index equation, did not significantly affect resting energy expenditure ($p=0.3$) or thermogenic effect of food ($p=0.7$) after adjustment for Tanner stage. In conclusion, our study did not find an association between insulin resistance and energy expenditure in obese children.

Keywords

obesity; insulin resistance; energy metabolism; calorimetry; pediatrics

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1. Introduction

Obesity in children is a growing epidemic in the United States and up to a third of school aged-children are overweight or obese [1]. Obesity is a multifactorial disease with underlying causes including genetic susceptibility and environmental factors. The thermic effect of food (TEF) is a loss of energy due to the active processing of food and accounts for approximately 10% of the daily energy expenditure [2]. Several studies in adults have shown that obese adults have a decreased TEF compared with non-obese adults, suggesting that obese adults may have a more efficient energy metabolism than normal weight adults [3, 4]. Insulin resistance has been postulated to further decrease TEF in adults, contributing to excess weight gain [3, 5].

Past studies have shown that obese children may have a reduced TEF after a high carbohydrate or high fat meal when compared with lean controls, but were limited by very small sample sizes of 6 obese girls [6] and 10 obese boys [7], respectively. It is unknown if insulin resistance further decreases TEF in obese children. Children have difficulty tolerating prolonged measurement of energy expenditure by indirect calorimetry using mouthpieces or hoods; therefore, there are few studies on TEF in obese children. In order to increase patient tolerance of indirect calorimetry, we utilized a whole-room indirect calorimetry chamber to measure resting energy expenditure and TEF in children with longstanding obesity. Our objective was to measure TEF in obese, non-diabetic children with varying degrees of insulin resistance. We hypothesized that TEF would decrease with increasing insulin resistance in these children.

2. Methods and Materials

2.1 Participants

Thirty-four children between 7 and 18 years old with a history of obesity onset prior to 10 years old (defined as body mass index (BMI) >95th percentile on Centers for Disease Control growth charts) were recruited at Vanderbilt University from November, 2010 through December, 2011, as previously described [8]. Exclusion criteria included diabetes, Cushing syndrome, Prader-Willi syndrome, growth hormone deficiency and use of metformin or other appetite altering drug in the past 3 months. Patients with well-controlled hypothyroidism were eligible to participate. Study visits were held at the Clinical Research Center (CRC) at Vanderbilt University (Nashville, TN, USA). All studies were approved by the Institutional Review Board of Vanderbilt University. Informed consent was obtained from all participants or a parent of the participant and assent was obtained from participants under 18 years old.

2.2 Anthropometrics

Standing height was measured using a wall-mounted stadiometer. Weight was measured using a digital scale, lightly clothed and without shoes. BMI was calculated using the equation $BMI = \text{weight (kg)} / \text{height (m)}^2$. BMI, height and weight z-scores were also calculated as standard deviations from the mean using gender and age specific Centers for Disease Control growth charts (www.cdc.gov/growthcharts/cdc_charts.htm). Fat mass was

measured by whole body dual energy x-ray absorptiometry using pediatric software (Lunar Prodigy, GE Medical Systems, Madison, WI, USA). Skeletal muscle mass was estimated using appendicular lean tissue mass (A_{LTM}) and organ/viscera tissue mass was estimated using non-appendicular lean tissue mass (NA_{LTM}) [9].

2.3 Laboratory assessment

A fasting blood sample was obtained for measurement of glucose (mg/dL), insulin (μ U/mL) and hemoglobin A1C. Insulin resistance was calculated using the homeostasis model assessment index equation ($HOMA-IR = \text{insulin} * \text{glucose}/405$) [10]. Patients were categorized as insulin resistant if the $HOMA-IR > 2.5$ [10].

2.4 Energy expenditure

Participants were asked to maintain their usual diet and abstain from vigorous exercise in the two days prior to the study visit. Participants arrived to the CRC in the fasting state. Energy expenditure was measured using a previously validated whole-room indirect calorimeter. This whole-room indirect calorimeter allows for precise measurement of energy expenditure on a minute by minute basis [11]. The accuracy of our room calorimeter for measuring energy expenditure by routine alcohol combustion tests was $99.2 \pm 0.5\%$ (mean $\pm$ SD) over 24 hours and $98.6 \pm 2.1\%$ over 30 minutes [12]. The system detects short-term changes in metabolic rate to 2.7% over 30 minutes and 0.6% over 2 hour measurement period. The room has precisely controlled temperature and humidity and is equipped with a window to the outside, window to the adjacent room, food pass window, sink, toilet, chair, and multimedia panel that includes TV. Participants were allowed to view movies, read, or use an iPad during the study. Participants rested quietly with minimal movement in a reclining chair for 30 minutes prior to measurement of resting energy expenditure (REE). Measurements were recorded in 1 minute intervals and REE was calculated over a 30 minute period from rates of oxygen consumption and carbon dioxide production using the Weir equation [13]. The percent predicted REE (measured REE/predicted REE) was calculated using the Molnar formula [14, 15]. Post-prandial fat oxidation was calculated using the equation $1.695 * VO_2 - 1.701 * VCO_2$ [16].

After measurement of REE, participants were given a high fat test meal (81% fat, 17% carbohydrate, 2% protein), standardized individually to provide 35% of the measured REE. The meal was consumed in less than 30 minutes and the remaining shake was weighed to determine calories consumed. Participants who consumed less than 80% of the shake were excluded from the analysis. TEF was calculated as the postprandial increase in energy expenditure above the REE over 180 minutes, expressed as percent of calories consumed during the test meal. Participants were directly observed by study personnel and asked to remain seated throughout the study. Only data from when participants were seated quietly with minimal movement as recorded minute-by-minute was included in the analysis.

2.5 Data collection

Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University [17]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.

2.6 Statistical analyses

Unless specified otherwise, data are expressed as median (lower quartile, upper quartile) and nonparametric tests were used. Mann-Whitney U-test was used for continuous variables and Fisher's exact test for categorical variables. Differences in percent predicted REE between Tanner stages was assessed using the Kruskal Wallis test, followed by Mann-Whitney U-test if overall significance was <0.05 . Multivariable models (linear regression) were limited to one covariate per 10 subjects to minimize risk of overfitting. Tanner stage was chosen as a covariate as previous research has shown a role of puberty in both energy expenditure and insulin resistance [18-21]. Statistical analysis was conducted using SPSS version 19.

3. Results

Thirty-four children participated in the study. Nine patients did not eat the test meal and were excluded. These patients were similar to the included subjects (age 12.7 years [10.8, 16.5], gender 55.6% female, BMI z-score 2.52 [2.24, 2.65], 22% insulin sensitive). Twenty five subjects had complete data available for analysis, 13 males and 12 females. The median age was 12.1 years old (range 7.7 – 17.9). Table 1 summarizes the baseline characteristics and the metabolic profiles of the insulin sensitive (n=6) and insulin resistant (n=19) groups. Two subjects had abnormal fasting glucose (103 mg/dL and 105 mg/dL) and five subjects had hemoglobin A1Cs in the pre-diabetes range (5.8% - 6.1%). None of the subjects were diagnosed with diabetes. The insulin resistant group had a significantly higher weight Z-score (3.0 (2.7, 3.4) vs. 2.3 (1.9, 2.8), $p=0.04$) but did not have a higher BMI Z-score (1.6 (1.0, 2.1) vs. 2.1 (1.9, 2.6), $p=0.11$) or percent body fat (48.1 (42.6, 52.1) vs. 45.0 (39.2, 49.8), $p=0.4$).

As expected, there was a significant decrease in percent predicted REE with increasing Tanner stage ($p=0.02$ by Kruskal-Wallis). The median percent predicted REE in the Tanner 1 group was 13% higher than the Tanner 5 group (122% (112, 131) vs. 109% (97, 115), $p=0.02$, $n=8$ per group). Each increase in Tanner stage was associated with a 122 kcal/day decrease in measured REE in a multivariable model adjusted for fat free mass (correlation coefficient 95% CI -225 to -19, $p=0.02$). This difference in measured REE was still significant after adjustment for NA_{LTM} (correlation coefficient 95% CI -183 to -9, $p=0.03$) but not A_{LTM} (correlation coefficient 95% CI -240 to 19, $p=0.09$). Females had higher percent predicted REE than males (112% (107, 124) vs. 103% (92, 110), $p<0.01$), however there was no difference in measured REE between males and females after adjusting for A_{LTM} (correlation coefficient 95% CI -346 to 124, $p=0.34$) or NA_{LTM} (correlation coefficient 95% CI -281 to 90, $p=0.3$). There was no difference in percent predicted REE between insulin sensitive and insulin resistant groups (Table 1). There was a significant decrease in measured REE in the insulin resistant group after adjustment for NA_{LTM} ($p=0.04$, Table 1), but this difference was eliminated after adjusting for Tanner stage ($p=0.13$).

Overall, we did not find a significant change in TEF with increasing insulin resistance. In multivariable models that adjusted for Tanner stage, HOMA-IR did not significantly affect TEF (correlation coefficient 95% CI -0.33 to 0.47, $p=0.7$). The results were not altered with the addition of gender to the model. There was not a significant effect of HOMA-IR on

percent predicted REE ($p=0.3$), post-prandial rate of fat oxidation (mg/kg/min , $p=0.5$) or respiratory quotient ($p=0.9$).

In a dichotomized model, there was no difference in TEF between insulin sensitive and insulin resistant children (2.77% (1.64, 4.02) vs. 2.80% (1.64, 4.27), $p=1.0$). To further probe these findings, we also used a second definition of insulin resistance, insulin level $>16 \mu\text{U}$ (upper limit of normal for the assay). In a dichotomized model, there was again no difference in TEF between insulin sensitive (insulin $<16 \mu\text{U}$, $n=12$) and insulin resistant (insulin $>16 \mu\text{U}$, $n=13$) children (2.27% (1.08, 3.41) vs. 2.90% (2.18, 4.47), $p=0.2$). There was no difference in TEF between males and females (2.99% (1.78, 4.24) vs. 2.60% (1.49, 4.07), $p=0.6$).

4. Discussion

We utilized a whole-room indirect calorimeter chamber to obtain energy expenditure data in obese children. We did not find a significant change in TEF with increasing insulin resistance. There is conflicting literature on the effect of insulin resistance on TEF in adults, with more recent articles demonstrating an inverse relationship [3-5]. However, it is unclear whether the decrease in TEF is the primary cause of obesity or whether it is a result of being obese. It is possible that insulin resistance, over time, leads to a compensatory decrease in metabolic rate which perpetuates the obesity and that children have not had a long enough exposure to obesity and insulin resistance to drive such changes. It is also possible that there is a small relationship between insulin resistance and TEF that we were unable to detect with our sample size. Since the cutoff for insulin resistance is arbitrary, we maximized our power by utilizing HOMA-IR as a continuous variable in a multivariable model. While our sample size of 25 subjects was larger than previously reported in the literature, it was not large enough for complex multivariable models without risk of overfitting.

Puberty and increasing age are associated with increasing insulin resistance [22]. While we did not use age specific cutoffs for HOMA-IR, we did adjust for Tanner stage in our multivariable model. It is possible that an increase in TEF during puberty masked a decrease in TEF, but this is unlikely as puberty is more typically associated with reduction in energy expenditure relative to lean mass [19, 20]. Accordingly, we found an inverse relationship between REE and Tanner stage after adjusting for fat free mass or NA_{LTM} which is thought to represent the organ/viscera mass. Lean mass accounts for the majority of variability in REE and organs such as the liver, brain, heart and kidneys have a particularly high metabolic rate. It is thought that the decrease in REE across age and puberty is due to a decrease in the rate of organ growth and a change in the proportion of organ mass to lean mass [18, 20]. A limitation of our study is the inclusion of multiple racial groups. It has been shown that REE is significantly higher in white children compared with African American children [19] however, there were slightly more African American children in the pre-pubertal group than the pubertal group which would not account for the higher REE of the pre-pubertal group.

A previous study in adults found increasing fat oxidation with increasing BMI after a high-fat meal [4]. Other studies utilizing different meal substrates have found no difference in fat

oxidation between obese and lean patients [23, 24]. In this study, the association between fat oxidation and obesity or insulin resistance was eliminated after adjusting for fat free mass. It is possible that 180 minutes is insufficient to measure energy response to a high-fat meal, however, this is the most commonly used time point in the literature and longer measurements are unlikely to be tolerated by children without compromising measurement accuracy [3, 7, 23, 25, 26]. It is estimated that 70% of TEF response occurs within 3 hours after the meal and this response is sufficient for comparative purposes [26-28].

It is important to understand the factors contributing to childhood obesity in order to develop effective treatments. We reject our original hypothesis and conclude that insulin resistance may not be associated with decreased energy expenditure in obese children. Other mechanisms besides insulin resistance may underlie abnormal weight gain in obese children. Limitations of this study include the sample size, inclusion of prepubertal and pubertal children as well as multiple ethnic groups, as detailed above. In addition, we used a high-fat test meal and results may differ with a high-protein or high-carbohydrate meal. Further studies are needed to confirm our findings.

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Abbreviation

BMI	body mass index
CRC	Clinical Research Center
HOMA-IR	homeostasis model assessment index equation
REE	resting energy expenditure
TEF	thermic effect of food

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Table 1

General Characteristics and Metabolic Profile

	Insulin Sensitive (n = 6)	Insulin Resistant (n = 19)	p- value
Age (years)	11.1 (9.9,12.8)	14.0 (10.5,15.3)	0.18
Gender (% female)	33	53	0.65
Race			
Caucasian	66.7% (n=4)	68.4% (n=13)	
African-American	16.7% (n=1)	21.1% (n=4)	
Asian	0%	5.3% (n=1)	
Hispanic	16.7% (n=1)	5.3% (n=1)	
Weight Z-score	2.3 (1.9, 2.8)	3.0 (2.7, 3.4)	0.04
Height Z-score	1.1 (1.0, 1.3)	1.6 (1.0, 1.6)	0.08
BMI Z-score	2.1 (1.9, 2.6)	1.6 (1.0, 2.1)	0.11
Body fat (%)	45.0 (39.2, 49.8)	48.1 (42.6, 52.1)	0.40
Hemoglobin A1C (%)	5.6 (5.3, 5.7)	5.5 (5.3, 5.7)	0.88
Fasting glucose (mg/dL)	92 (85, 96)	94 (90, 98)	0.48
Fasting insulin (mcU/mL)	5 (2, 7)	24 (14, 39)	<0.01
Tanner stage 1 (%)	50	26	0.34
REE _{%predicted}	122 (112, 131)	113 (107, 120)	0.60
REE _{ALTM}	110 (105, 140)	98 (83, 124)	0.12
REE _{NALTM}	100 (93, 117)	81 (73, 101)	0.04
TEF (%)	2.77 (1.64, 4.02)	2.80 (1.64, 4.27)	1.0
RQ	0.90 (0.80, 0.91)	0.86 (0.83, 0.90)	0.69
Fat oxidation (mg/kg/min)	80.1 (67.5, 135.8)	110.5 (83.6, 153.1)	0.37

Insulin resistant was defined as HOMA-IR >2.5. Measured REE was compared with the predicted REE by the Molnar formula (REE_{%predicted}) or adjusted for appendicular lean tissue mass (AL_{TM}) and for non-appendicular lean tissue mass (NAL_{TM}). Data expressed as median (lower quartile, upper quartile). P-value was calculated using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. BMI, height and weight Z-scores were calculated as standard deviations from the mean using gender and age specific 2000 Centers for Disease Control and Prevention growth charts. BMI, body mass index; HOMA-IR, homeostasis model assessment index of insulin resistance; REE, resting energy expenditure; TEF, thermogenic effect of food.