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Insulin sensitivity indices of glucose and free fatty acid metabolism in obese children and adolescents in relation to serum lipids

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Abstract

Objective: Most studies concerning the association between insulin resistance and the features of metabolic syndrome in obese children are based on measurement of insulin sensitivity indices (ISI) of glucose metabolism and not of fat metabolism.
Methods: We studied fasting low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, insulin, free fatty acids (FFA), blood glucose, ISI of glucose (homeostasis model assessment [HOMA] %S), and FFA metabolism (ISI-FFA) in 124 obese children aged 6 to 16 years. ISI-FFA was calculated based on the formula 2/(insulin × FFA + 1). Stepwise forward regression analyses were performed with triglycerides, HDL-C and LDL-C as dependent variables and age, sex, stage of puberty, body mass index, insulin, FFA, and blood glucose as independent variables. Direct multiple regression analyses were conducted with the dependent variables triglycerides, HDL-C, and LDL-C including age, sex, stage of puberty, body mass index, HOMA %S, and ISI-FFA as independent variables. Furthermore, ISI-FFA was measured in 13 normal-weight children aged 6 to 16 years.
Results: ISI-FFA (median 0.30) was significantly ($P < .05$) reduced in obese children compared with normal-weight children (median ISI-FFA 0.64). In stepwise regression analyses, triglycerides were significantly correlated with insulin and FFA ($P < .05$), LDL-C levels were significantly correlated with FFA ($P < .05$), and HDL-C was related to stage of puberty ($P < .05$), whereas all other variables demonstrated no significant associations with triglycerides, LDL-C, and HDL-C levels. In contrast to HOMA %S, ISI-FFA was significantly ($P < .05$) related to triglycerides and LDL-C in direct multiple regression analysis.
Conclusions: Insulin resistance in respect to FFA metabolism is already detectable in childhood. Insulin sensitivity index of FFA metabolism seems to be a better tool for describing insulin resistance in lipid metabolism than ISI of glucose metabolism, because FFA and partially insulin but not glucose were related to triglycerides and LDL-C.

1. Introduction

The increasing prevalence of obesity in childhood and adolescence poses an ever-increasing health problem [1]. Some obese subjects go on to display a characteristic metabolic profile of reduced high-density lipoprotein cholesterol (HDL-C), increased low-density lipoprotein cholesterol (LDL-C) and triglycerides, and insulin resistance (metabolic syndrome) [2,3]. Early features of the metabolic syndrome and insulin resistance may be demonstrated in some obese subjects as early as during childhood [4]. Many studies in childhood demonstrated a connection between parameters of insulin sensitivity and dyslipidemia [5,6].

These studies concerning the association between insulin resistance in obese children and the features of metabolic syndrome were performed analyzing glucose metabolism using clamp studies [7] or insulin sensitivity indices (ISI) with regard to glycemia [2-5]. On the other hand, insulin regulates not only glucose but also free fatty acids (FFA) metabolism in addition to other metabolic pathways. In insulin resistance, there is abnormal fatty acid metabolism in skeletal muscle and altered intestinal absorption of fatty acids [8,9].

Insulin resistance in glucose metabolism does not necessarily mean insulin resistance in respect to FFA metabolism [10,11]. Studies analyzing the association between lipids and ISI based on FFA metabolism are missing so far in childhood.

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Therefore, we studied the association between ISI of glucose and FFA metabolism and compared their relationships with lipids in obese children and adolescents.

2. Materials and methods

We studied ISI and lipid parameters in 124 obese children and adolescents aged 6 to 16 years of the outpatient clinic for obesity in the Vestische Kinder-und Jugendklinik Datteln, Germany. Children with endocrine disorders, familial hyperlipidemia, or syndromal obesity were excluded from the study. Obesity was defined by body mass index (BMI) for age above BMI 97th percentile for German children and adolescents [12]. The BMI 97th percentile reaches BMI values of 30 kg/m^2 at the age of 18 years according to the definition of obesity in childhood of the International Task Force of Obesity [13]. The weight status was recorded as BMI and the BMI standard deviation score (SDS-BMI) using the LMS method, which summarizes the data in terms of 3 smooth age curves called L (lambda), M (mu), and S (sigma) [12,13]: The M and S curves correspond to the median and coefficient of variation BMI for German children at each age and sex, whereas the L curve allows for the substantial age-dependent skewness in the distribution of BMI. The assumption underlying the LMS method is that after Box-Cox power transformation, the data at each age are normally distributed [13].

In the fasting state, HDL-C and LDL-C were measured by an enzymatic test (LDL-C Plus and HDL-C Plus, respectively; Roche Diagnostics, Mannheim, Germany), and triglycerides were measured by a colorimetric test (Vitros Trig-Analyseplättchen, Neckargemuend, Germany). Fasting insulin was measured by microparticle enzyme assay (Abboth, Bau Nauheim, Germany). Fasting blood glucose and FFA were determined by colorimetric tests (Vitros GLU-Analyseplättchen, respectively, WAKO Freie Fettsäure). Intraassay and interassay coefficients of variation were <10% in all methods. Cutoff points of 3.4 mmol/L (130 mg/dL) for LDL-C, 0.9 mmol/L (35 mg/dL) for HDL-C, and 1.7 mmol/L (150 mg/dL) for triglycerides were used according to international guidelines to define dyslipidemia [14].

Homeostasis model assessment (HOMA) [15] was used to detect the degree of insulin sensitivity in glucose metabolism: the sensitivity can be assessed from the fasting glucose and insulin concentrations by the formula: sensitivity (HOMA %S) = 22.5/(insulin [mU/L] × glucose [mmol/L]). Insulin sensitivity for blood FFA (ISI-FFA) can be calculated with the formula: 2/(insulin [mU/L] × FFA [mmol/L]) +1) [16]. The ISI-FFA and HOMA %S were already validated in clamp studies in children [17]. They both represent simple tools suitable for clinical studies, allowing assessment of whole-body insulin sensitivity with regard to both glycemia and blood FFA [10]. The lower limit of the interquartile range for HOMA %S in healthy normal-weight children depends on pubertal stage and sex (prepubertal boys, 0.87; pubertal boys, 0.49; prepubertal girls, 0.78; pubertal girls, 0.44) [18]. The mean normal value for ISI-FFA is approximately 1 with maximal variations compromised between 0 and 2 [10,16].

Furthermore, fasting FFA, blood glucose, and insulin were measured in 13 normal-weight children. ISI-FFA and HOMA S% were calculated in these subjects.

The pubertal developmental stage was determined according to Marshall and Tanner and categorized into 2 groups: prepubertal: boys with pubic hair and gonadal stage I and girls with pubic hair stage and breast stage I; pubertal: boys with pubic hair and gonadal stage ≥II and girls with pubic hair stage and breast stage ≥II.

Statistical analyses were performed by Winstat. Pearson correlation was determined between serum insulin, FFA, and blood glucose. Furthermore, FFA was correlated to HOMA %S by Pearson correlation. Triglycerides, LDL-C, and HDL-C were correlated to age, degree of overweight (SDS-BMI), insulin, FFA, ISI of glucose (HOMA %S), and FFA metabolism (ISI-FFA) by Pearson correlation. To study the relationships between insulin indices and lipids, direct multiple linear regression analyses were performed with triglycerides, HDL-C, and LDL-C as dependent variables and age in years, sex, stage of puberty, degree of overweight (BMI), ISI of glucose (HOMA %S), and ISI-FFA metabolism as independent variables in each model. To study the relationships between FFA, blood glucose, insulin concentrations, and lipids, multivariate stepwise forward regression analyses were performed with triglycerides, HDL-C, and LDL-C as dependent variables and age in years, sex, stage of puberty, degree of overweight (BMI), insulin concentrations, blood glucose levels, and FFA as independent variables in each model. Sex and stage of puberty were used as classification variables in each model. Age, insulin, FFA, blood glucose, HOMA %S, and ISI-FFA were compared between the 124 obese children and 13 normal-weight children using Kruskal-Wallis test. Sex and pubertal stage were compared in these 2 groups by χ^2 test. A $P < .05$ was considered as significant. The study was approved by the local Ethics Committee of the University of Witten-Herdecke. Informed consent was obtained in all participants and their parents.

3. Results

Anthropometrical data and ISI of glucose and FFA metabolism of the 124 obese and 13 normal-weight children are demonstrated in Table 1. The obese and normal-weight children did not differ in terms of age, sex, and stage of puberty. Eighty-six (69%) of the obese children had HOMA %S below the interquartile range of healthy children adjusted for sex and pubertal stage. HOMA %S and ISI-FFA were significantly reduced in the obese compared with the normal-weight children (Table 1).

In the obese children, triglycerides were in median 107 (interquartile range, 77-154) mg/dL, LDL-C levels were in

Table 1
Anthropometrical data and parameters of glucose and fat metabolism in 124 obese and 13 normal-weight children

	Obese	Normal weight	*P*
Age (y)	10.5 (8.2-12.3)	10.5 (7.5-12.6)	.961
Sex	47% Boys	54% Boys	.954
Pubertal stage	51% Prepubertal	54% Prepubertal	.739
Weight (kg)	59.9 (44.4-74.5)	44.0 (25.5-48.8)	<.001
BMI (kg/m^2)	26.7 (24.1-28.8)	19.3 (15.3-20.8)	<.001
SDS-BMI	2.31 (2.07-2.70)	0.14 (−0.51 to 1.04)	<.001
Insulin (mU/L)	13.9 (9.1-17.9)	7.3 (3.5-10.0)	<.001
FFA (mmol/L)	0.46 (0.35-0.61)	0.37 (0.20-0.47)	.037
Glucose (mmol/L)	5.0 (4.7-5.3)	4.8 (4.6-5.0)	.208
HOMA %S	0.32 (0.24-0.49)	0.64 (0.60-1.17)	<.001
ISI-FFA	0.30 (0.20-0.42)	0.63 (0.48-0.81)	<.001

Data as median and interquartile range.

median 103 (interquartile range, 82-120) mg/dL, and HDL-C levels were in median 46 (interquartile range, 41-53) mg/dL. Twenty (16%) children showed LDL-C levels above 130 mg/dL, 33 (27%) had triglycerides above 150 mg/dL, and 8 (7%) had HDL-C below 35 mg/dL.

Serum insulin levels were not significantly correlated to FFA ($r = -0.08$, $P = .181$) and blood glucose ($r = 0.08$, $P = .183$). FFA did not significantly correlate to blood glucose ($r = -0.03$, $P = .378$) and HOMA S% ($r = 0.14$, $P = .058$).

Triglycerides correlated significantly to insulin ($r = 0.19$, $P = .018$), HOMA %S ($r = -0.24$, $P = .003$), FFA ($r = 0.19$, $P = .019$), and ISI-FFA ($r = -0.30$, $P < .001$), whereas there were no significant correlations to SDS-BMI ($r = 0.01$, $P = .500$) and age ($r = 0.04$, $P = .314$).

LDL-C correlated significantly to FFA ($r = 0.20$, $P = .015$), whereas there were no significant correlations to SDS-BMI ($r = -0.12$, $P = .097$), age ($r = -0.08$, $P = .176$), insulin ($r = -0.09$, $P = .154$), and ISI of both glucose (HOMA %S) ($r = 0.01$, $P = .492$) and FFA metabolism (ISI-FFA) ($r = -0.11$, $P = .116$).

HDL-C correlated significantly to HOMA %S ($r = 0.15$, $P = .048$), SDS-BMI ($r = -0.20$, $P = .012$), and age ($r = -0.14$, $P = .048$), whereas there were no significant correlations to insulin ($r = -0.14$, $P = .065$), FFA ($r = 0.02$, $P = .424$), and ISI-FFA ($r = 0.12$, $P = .099$).

In direct multiple linear regression analyses (see Table 2), triglycerides and LDL-C were significantly correlated to ISI-FFA, whereas there were no significant correlations to insulin index of glucose metabolism (HOMA %S). HDL-C correlated significantly to age, stage of puberty, and degree of overweight in direct multiple linear regression, whereas there were no significant correlations to HOMA %S and ISI-FFA.

In stepwise forward multivariate regression analysis using age, sex, stage of puberty, degree of overweight (BMI), insulin, blood glucose, and FFA as independent variables in each model, triglycerides were significantly ($P < 0.05$) correlated with insulin and FFA, LDL-C levels were significantly ($P < 0.05$) correlated with FFA, and HDL-C was significantly ($P < .05$) related to stage of puberty, whereas all other variables in the models were not significantly associated with triglycerides, LDL-C, and HDL-C levels (Table 3).

Table 2
Direct multiple linear regression analyses with triglycerides, LDL-C, and HDL-C as dependent variables

Independent variable	Coefficient	95% Confidence interval +/−	*P*
Triglycerides as dependent variable ($r^2 = 0.35$)			
Constant	+269	+148 to +390	<.001
Age (y)	−2.82	−10.01 to +5.34	.493
Sex	+3.94	−23.37 to +31.25	.775
Puberty	+20.6	−19.3 to +60.3	.301
BMI	−3.03	−7.33 to +1.27	.166
HOMA %S	−19.2	−74.9 to +36.5	.431
ISI-FFA	−120	−227 to −13	.028
LDL-C as dependent variable ($r^2 = 0.34$)			
Constant	+194	+139 to +248	<.001
Age (y)	−1.56	−4.18 to +2.51	.395
Sex	+6.23	−6.01 to +18.45	.314
Puberty	+14.8	−3.2 to +32.4	.100
BMI	−2.53	−4.48 to +0.56	.012
HOMA %S	+7.00	−16.14 to +31.87	.578
ISI-FFA	−49.7	−97.7 to −1.3	.043
HDL-C as dependent variable ($r^2 = 0.43$)			
Constant	+59	+45 to +73	<.001
Age (y)	−1.04	−1.97 to −0.11	.030
Sex	−2.23	−1.02 to −5.39	.164
Puberty	−6.59	−11.14 to −2.02	.005
BMI	−0.63	−1.14 to −1.13	.015
HOMA %S	+1.86	−5.41 to +8.29	.569
ISI-FFA	−3.71	−16.15 to +8.75	.557

n = 124; sex: 0, man; 1, woman; puberty: 0, prepubertal; 1, pubertal.

Table 3
Stepwise forward regression analyses with triglycerides, LDL-C, and HDL-C as dependent variables and age, sex, stage of puberty, BMI, FFA, blood glucose, and insulin as independent variables in each model

Dependent variable	Selected variables	Regression coefficient (95% confidence interval)	*P*	r^2
Triglycerides	Insulin	0.94 (0.17-1.71)	.018	0.27
	FFA	72 (7-137)	.031	
LDL-C	FFA	34 (4-64)	.030	0.20
HDL-C	Puberty	−5.3 (−8.2 to −2.1)	.001	0.29

n = 124, sex: 0, men; 1, women; puberty: 0, prepubertal; 1, pubertal.

4. Discussion

This is the first study in childhood comparing the relationships between lipids and insulin sensitivity of both glucose and FFA metabolism. The obese children demonstrated significantly lower HOMA S% and ISI-FFA compared with the normal weight controls of same age, sex, and stage of puberty. The ISI-FFA levels of our children were similar compared with the decreased levels in studies of obese adults [10,11]. Since hypertriglyceridemia, increased LDL-C, and insulin resistance in both glucose and FFA metabolism were frequently present in our sample of obese

children, it is possible to analyze the relationships between these lipids and the different ISI.

Because both FFA and blood glucose depend on insulin levels, and on the other hand, blood glucose influences insulin levels [19], calculations of direct correlations between lipids, insulin, and FFA are difficult to interpret. Insulin sensitivity indices such as HOMA %S and ISI-FFA take into consideration these relationships. Clamp studies are the gold standard to measure insulin sensitivity [19]. Because the insulin index HOMA %S correlated well to clamp studies and has low coefficients of variation [17,19], this measurement used in our study is a well-established method to study insulin sensitivity of glucose metabolism in field studies. Validation of ISI-FFA in clamp studies is difficult to perform because clamp studies are carried out under persistent hyperinsulinemia as never occurs in the life of the patients and which entails FFA suppression [10].

FFA related to insulin is a good marker of fat metabolism in insulin resistance. Serum FFA concentrations reflect a balance between release (from the intravascular lipolysis of triglyceride-rich lipoproteins and lipolysis of adipose tissue triglycerides stores) and uptake (predominantly reesterified in liver and oxidized in muscle, heart, liver, and other tissues) [9]. In insulin resistance, there is defective esterification and reesterification of fatty acids in liver, as well as reduced insulin-mediated suppression of hormone-sensitive lipase in adipose tissue [20,21], the rate-limiting enzyme for FFA mobilization of adipose tissue triglycerides stores [9]. FFA are released from triglycerides of chylomicrons and very low–density lipoproteins (VLDL) through the action of lipoprotein lipase which is also insulin-mediated [22]. Furthermore, the uptake and oxidation of FFA are diminished in skeletal muscle of insulin-resistant subjects [23]. Accordingly, fasting plasma FFA have been found to be elevated in insulin-resistant obese individuals [8,9].

Because we measured impairment of both FFA and glucose metabolism already in obese children, this seems to confirm the hypothesis of a link between insulin resistance in glucose and fat metabolism [11]. The elevated FFA flux from an expanded adipose tissue to nonadipose tissue in insulin resistance has been reported to have a deleterious effect on insulin regulation of carbohydrate metabolism [9]. Three possible mechanisms are discussed [9,20,24,25]: a fat-related inhibition of glucose transport, a decrease in muscle glycogen synthase activity, and a decrease in glucose oxidation (Randle hypothesis). According to this, prospective studies have suggested that elevation of plasma FFA is an independent predictor of progression to type 2 diabetes [26,27]. We measured no significant correlation between FFA and HOMA %S in concordance with one previous study [18]. Probably, the measurement of FFA uptake or oxidation would reflect better tools to describe the link between insulin resistance in both fat and glucose metabolism.

Pearson correlations between triglycerides, LDL-C, HDL-C, and parameters of both glucose and FFA metabolism (FFA, insulin, HOMA S%, and ISI-FFA) were not significant or only very weak in our study. This is in agreement with other studies [2-5]. Therefore, they hold no predictive value. Because lipids are influenced not only by glucose or FFA metabolism but also by other factors such as age, sex, stage of puberty, or degree of overweight [2,4,5], multiple regression analyses adjusted for these factors are necessary to analyze the relationships between lipids and parameters of both glucose and FFA metabolism.

Triglycerides and LDL-C levels were correlated in direct multiple linear regression analyses to insulin index of FFA metabolism (ISI-FFA) but not to insulin index of glucose metabolism (HOMA %S). Therefore, ISI-FFA seems to reflect a better method than HOMA %S for describing the insulin resistance in lipid metabolism. Furthermore, FFA and insulin levels were identified as significant independent parameters of triglycerides concentrations in forward stepwise regression analysis pointing to advantages of ISI-FFA to single correlations of FFA or insulin with triglycerides.

The increased flux of FFA from intra-abdominal adipose tissue is a major reason for the hypertriglyceridemia in insulin resistance [20]. In the liver, increased FFA flux drives the triglyceride-rich VLDL synthesis and secretion [9,20]. The great majority of fatty acids of VLDL triglycerides come from FFA [28]. Furthermore, hypertriglyceridemia in insulin-independent diabetes with fasting hyperglycemia is associated with increased hepatic VLDL triglycerides secretion because of insulin resistance [29]. In insulin-resistant hypertriglyceridemic individuals, a vicious cycle may be set up: increased circulating VLDL levels lead to increased FFA flux to the liver, which then stimulates a further increase in VLDL production [20]. Furthermore, hypertriglyceridemia is related to the critical role of insulin in the production and clearance of triglyceride-rich lipoproteins from the plasma [30]. In peripheral tissues, insulin deficiency results in impaired lipoprotein lipase activity and diminished clearance of triglyceride-rich particles [22].

An increase in LDL-C levels in obese children and adults did not correlate to ISI of glucose metabolism [31-34]. This is in agreement with the results from our study demonstrating no significant relationship between HOMA S% and LDL-C concentrations in multiple linear regression analysis. Elevated LDL-C levels are regarded as an effect of fat-rich diet and polygenic disposition [35]. However, LDL-C correlated significantly in our study with the ISI-FFA metabolism. On the other hand, stepwise forward regression analysis identified only FFA but not insulin levels as an independent significant parameter of LDL-C levels. Therefore, calculation of ISI-FFA seems not to represent any advantages to FFA serum concentrations in displaying the relationships between LDL-C and FFA metabolism. This is in line with the studies demonstrating that LDL levels are mostly independent of indices of insulin resistance but increase because of an increased VLDL biosynthesis caused by an increased flux of FFA to the liver [31,34-36].

HDL-C did not significantly correlate to FFA, insulin levels, and neither HOMA %S nor ISI-FFA in direct multiple

and stepwise forward regression analyses. These results are in contrast to studies in adults and adolescents [2,3] demonstrating that the production of HDL-C is connected to the degradation of VLDL particles, which is decreased in insulin resistance [37]. A decrease in HDL-C has been described predominantly in adolescents and adults but not in children [38]. The measured effect of age and stage of puberty on HDL-C levels in our study is in concordance with these findings. Because lower than 10% of the children in our study had decreased HDL-C levels, this may explain the missing correlations between ISI and HDL-C. Therefore, our study sample probably is not ideal to analyze the relationships between HDL-C and parameters of insulin resistance.

In summary, ISI-FFA metabolism seems to be a better tool for describing insulin resistance in lipid metabolism (especially in hypertriglyceridemia) than ISI glucose metabolism. Most importantly, insulin resistance in respect to FFA metabolism in obese children is already detectable in childhood and early adolescence.

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