

Effect of Changes in Fat Distribution on the Rates of Change of Insulin Response in Children

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Abstract

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Objective: To develop mixed models for examining longitudinal associations between rates of change in visceral, subcutaneous abdominal, and total body fat with rates of change in fasting insulin (FI) and insulin sensitivity (SI) over 3 years in children.

Research Methods and Procedures: Seventy-seven children (mean age, 8.3 years at baseline) from Birmingham, Alabama, with three or more annual measures of FI and SI were included. Abdominal fat was measured by computed tomography, and total body fat and lean tissue mass were measured by DXA. Mixed models examined the longitudinal associations between the baseline level/rate of change of different fat compartments and the rate of change in FI or SI.

Results: An annual increase of ~5% in FI was associated with 1 cm²/yr of visceral fat gain per year ($p < 0.05$), independent of subcutaneous abdominal fat. A 1-cm² difference in initial subcutaneous abdominal fat was associated with an ~0.2% increase per year in FI ($p < 0.02$), independent of visceral fat. None of the rates of change in any of the fat measures was associated with the rate of change of SI.

Discussion: The rate of change in visceral fat was positively

associated with the rate of change in FI, independent of increasing subcutaneous abdominal fat; however, subcutaneous abdominal fat may be more predictive of the rate of change of FI than visceral or total fat. Therefore, growth-related increases in abdominal fat, particularly subcutaneous abdominal fat, may contribute to accelerating increases in FI, but have no effect on SI.

Key words: body composition, fat distribution, fasting insulin, insulin sensitivity

Introduction

To our knowledge, there have been no longitudinal studies of children that examined the relationship between the different compartments of body fat and fasting insulin or insulin sensitivity using precise measures of insulin sensitivity and body composition. In addition, most studies have reported correlations but not addressed the independent effects of discrete body-fat compartments on fasting insulin or insulin sensitivity.

Therefore, the aim of this study was to determine whether baseline or longitudinal changes in visceral fat, subcutaneous abdominal fat, or total body fat were associated with changes in fasting insulin and insulin sensitivity during pre- and early-pubertal growth in white and African-American children. Based on our previous cross-sectional findings, we hypothesized that visceral fat would be significantly related to fasting insulin but not insulin sensitivity over time, whereas subcutaneous abdominal fat and total body fat would be significantly related to insulin sensitivity but not fasting insulin over time. In addition, we hypothesized that these relationships would be consistent between the two races and the two genders.

Research Methods and Procedures

Subjects

Children were recruited by newspaper and radio advertisements and by word of mouth. Subjects were screened by

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medical history and were ineligible if they were 1) <4 years of age, 2) taking medications known to affect body composition or physical activity (e.g., prednisone, Ritalin, or growth hormone), 3) previously diagnosed with syndromes known to affect body composition or fat distribution (e.g., Cushing's syndrome, Down's syndrome, insulin-dependent diabetes, or hypothyroidism), or 4) diagnosed previously with any major illness. Because the intent of the study was to recruit a heterogeneous group of children, there were no criteria for other characteristics such as obesity. This study was approved by the Institutional Review Board of the University of Alabama at Birmingham. Parents provided informed consent before testing began.

Protocol and Measurements of Body Composition

Children were admitted to the General Clinical Research Center (GCRC; University of Alabama at Birmingham) in the late afternoon for an overnight visit. On arrival, anthropometric measurements (including sexual maturity) were obtained and dinner was served at ~5:00 PM. An evening snack was allowed, but only water and energy-free, non-caffeinated beverages were permitted after 8:00 PM until after the morning testing. Between 7:00 and 8:00 PM, a single-slice computerized tomography scan (120 kVp, variable mA, 1.0-second scan time, 5-mm slice thickness; GE Hi-speed; GE Medical Systems, Milwaukee, WI) was taken at the level of the umbilicus for the measurement of visceral fat and subcutaneous abdominal fat using the density-contour program of the scanner software as described previously (1). After an overnight fast, blood was collected for hormone analysis the next morning, and a tolbutamide-modified frequently sampled intravenous glucose tolerance test was performed. Two weeks later, the children arrived at the Energy Metabolism Research Unit at 7:00 AM while in a fasted state, and total body fat and lean tissue mass were determined by DXA with a Lunar DPX-L densitometer (Lunar Corp., Madison, WI) that was validated previously in the pediatric body-weight range (2,3). Using an identical protocol, the current study was carried out for 3 consecutive years with a measure at baseline and a follow-up exam conducted each ensuing year.

Assessment of Sexual Maturation

Tanner's criteria were used to estimate sexual maturation on a scale of 1 to 5, with stage 1 being prepubertal and 5 being adult. Qualified pediatricians assessed Tanner Stage in all the children.

Tolbutamide-Modified Frequently Sampled Intravenous Glucose-Tolerance Test

At 6:00 AM the morning after GCRC admission, a topical anesthetic (Emla cream; AstraZeneca, Wilmington, DE) was applied to the antecubital space of both arms, and at 7:00 AM, flexible intravenous catheters were placed. Three

blood samples (2 mL) were drawn for determination of basal glucose and insulin. At time 0, glucose (25% dextrose; 11.4g/m²) was administered intravenously. Blood samples (2 mL) were then collected at the following times relative to glucose administration at minute 0: 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180. Tolbutamide (125 mg/m²) was injected intravenously at 20 minutes. Sera were analyzed for glucose and insulin, and values were entered into the MINMOD computer program (version 3.0) for determination of insulin sensitivity (4–6).

Assay of Glucose and Insulin

Glucose was measured in 10 μ l of sera using Ektachem DT II System (Johnson and Johnson Clinical Diagnostics, Rochester, NY). In our laboratory, this analysis had a mean intra-assay CV of 0.61% and a mean inter-assay CV of 1.45%.

Insulin was assayed in duplicate 200- μ l aliquots with Coat-A-Count kits (Diagnostic Products, Los Angeles, CA). According to the supplier, cross-reactivity of this assay with proinsulin is 40% at mid-curve; C-peptide was not detected. In our laboratory, this assay had a sensitivity of 11.4 pM (1.9 μ IU/mL), a mean intra-assay CV of 5% and a mean inter-assay CV of 6%. Commercial quality-control sera of low, medium, and high insulin concentration (Lyphochek Bio-Rad, Anaheim, CA) were included in every assay to monitor variation over time.

Statistical Analysis

Our sample for analysis included children with at least three annual measures of insulin sensitivity, fasting insulin, and body fat ($n = 77$ children; 301 total observations). Children were studied annually, and, on average, each child was measured 3.9 times during the study (annually over ~3 years).

A mixed-model approach (Proc Mixed in SAS) was designed to examine the associations between rates of change in fat compartments and rates of change in insulin measures. This approach uses random coefficients and allows nesting repeated measures within subjects while controlling for time-variant, within-subject covariates. A two-stage approach was used to test our hypotheses. In the first stage, each of the fat measures was regressed on time to obtain parameter estimates of the rate of change (i.e., slope) and baseline value/projected time-zero value (i.e., intercept) of fat for each individual. In the second stage, these intercepts and slopes were entered into another set of mixed models, where fasting insulin or insulin sensitivity were the dependent variables, as fixed effects. This two-stage procedure allowed for the simultaneous testing of the hypotheses that baseline fat and/or change of fat over time was significantly related to the change of fasting insulin or insulin sensitivity over time.

Specifically, in the first stage of analysis, estimates (solutions unique to each individual) of the baseline level and

slope (i.e., rate of change) of visceral fat, subcutaneous abdominal fat, and total body fat over time were generated first from three separate models regressing each of the three fat measures against time alone. No covariates were entered at this stage. The basic structure of a mixed model is illustrated as follows, using the growth of visceral fat as an example:

```
PROC MIXED;
  CLASS Patient_ID Visit_Number;
  MODEL Visceral_Fat = Time/SOLUTION DDFM =
  BW;
  RANDOM Intercept Time/SUBJECT = Patient_ID
  TYPE = UN;
  REPEATED Visit_Number/SUBJECT = Patient_ID
  TYPE = AR(1);
  RUN;
```

In this model, the “time” variable represented the precise number of years since baseline was used to estimate the rate of change of visceral fat (i.e., change in visceral fat per year). The intercept and slope of visceral fat were allowed to vary randomly for each individual. In other words, a unique pattern of visceral fat change was drawn for each individual. The intercept was defined at baseline and represented the baseline level of visceral fat. Visit number was used to align the repeated observations systematically. The covariance structure of the intercept and slope was set as unconstrained and the covariance structure of the repeated visceral fat measures was set as autoregressive with a lag of one. Between-/within-subjects degree of freedom was used. The same model was used to generate unique intercepts and slopes of subcutaneous abdominal fat and total body fat for each individual. These intercepts and slopes were then treated as the independent fixed effect in the second stage of analysis.

In the second stage of analysis, fasting insulin and insulin sensitivity were \log_e transformed to obtain normality. Using six separate models, we regressed fasting insulin and insulin sensitivity on the previously obtained intercepts and slopes of visceral fat, subcutaneous abdominal fat, and total body fat. Age at the first visit was entered into the models as a fixed covariate to account for the range of ages when children first enrolled in the study. Race and gender (both dichotomous) and Tanner Stage (ordinal) were also entered as fixed covariates. In addition, when visceral fat was the independent variable, subcutaneous abdominal fat was entered as a covariate to examine the unique contribution of visceral fat in the abdomen relative to that of subcutaneous fat. When subcutaneous abdominal fat was the independent variable, visceral fat was entered as a covariate to examine the unique contribution of subcutaneous fat in the abdomen relative to visceral fat. When total body fat was the independent variable, lean-tissue mass was entered as a covariate to examine the contribution of fat gain beyond what was expected from normal growth. These covarying adipose-/lean-tissue measures were considered time-variant and cen-

tered at the appropriate sample mean. All main effects (noninteractions) in the models represented relations with the initial status of the dependent outcome.

To address the aim of this study, two-way interactions were created between time and both the baseline level of a fat depot and the rate of change of a fat depot. These interaction terms were the primary variables of interest. For example, the interaction of initial visceral fat and time was used to test the effect of initial visceral fat on the rate of change of either fasting insulin or insulin sensitivity. The interaction of the rate of change of visceral fat and time was used to test the longitudinal association between change in visceral fat and change in fasting insulin or insulin sensitivity over time. In addition to the interaction between time and the fat variables, respective two-way interaction terms between time and baseline age, race, gender, Tanner Stage, or adipose-/lean-tissue covariates were used to adjust for their effect on the rate of change of the dependent outcome. Furthermore, to examine whether the relationships between the baseline level or the rate of change of a fat compartment and the rate of change of either fasting insulin or insulin sensitivity differed in terms of race, gender, or Tanner Stage, six triple interaction terms were created respectively [i.e., initial “fat” \times time \times (gender, race, or Tanner Stage) and “rate of change of fat” \times time \times (gender, race, or Tanner Stage)].

Aside from the change of parameters, model specifications in the second stage of analysis were the same as those in the first stage. Namely, time and intercept were treated as random effects in all models. In addition, between-/within-subjects degree of freedom was selected and the covariance structure in the random statement was left as unconstrained. In the repeated statement, an autoregressive covariance structure with a time lag of one was used.

All procedures were conducted using SAS v.8.01 (SAS Institute Inc., Cary, NC) and all statistical tests had a type I error set at $p = 0.05$.

Results

Table 1 shows the characteristics of the sample at baseline and at 3 years by gender and race. By the end of the study, over half of the children remained at Tanner Stage 1 or 2, 15 of the children were at Tanner Stage 3, and 2 were at Tanner Stage 4.

Effects of Fat on the Rate of Change of Fasting Insulin

There was a significant interaction between the rate of change in visceral fat and time ($\beta = 0.05 \pm 0.02$, $p < 0.05$), after adjusting for subcutaneous abdominal fat and other covariates (Table 2). This suggests that with every 1-cm² increase in visceral fat per year, there would be a 5% increase in fasting insulin per year (i.e., because the analysis was performed on a \log_e scale, a percentage increase in the

Table 1. Subject characteristics at baseline and at 3 years

Characteristics	African-American	White	African-American	White
	girls (n = 22)	girls (n = 17)	boys (n = 20)	boys (n = 18)
Age (years)	8.4 ± 2.0	8.4 ± 1.5	7.9 ± 1.5	8.4 ± 1.6
	11.1 ± 1.9	10.9 ± 1.6	11.0 ± 1.5	11.3 ± 1.7
Visceral fat (cm ²)	26.3 ± 14.8	34.8 ± 19.9	36.7 ± 31.7	31.7 ± 20.8
	29.8 ± 18.5	44.1 ± 25.1	38.9 ± 31.5	37.2 ± 19.4
Subcutaneous abdominal fat (cm ²)	100.9 ± 93.8	108.3 ± 79.5	105.2 ± 130.4	103.1 ± 99.0
	160.5 ± 138.9	176.9 ± 139.0	125.4 ± 130.2	109.8 ± 87.6
Total body fat (kg)	11.9 ± 8.1	10.2 ± 5.6	11.4 ± 8.5	9.7 ± 6.8
	15.8 ± 11.3	17.6 ± 12.1	18.4 ± 15.2	13.1 ± 9.5
Lean tissue (kg)	22.1 ± 6.2	20.5 ± 4.9	23.3 ± 5.1	22.1 ± 5.3
	32.9 ± 7.5	29.9 ± 8.5	34.5 ± 7.9	32.1 ± 9.5
Body mass index (kg/m ²)	19.3 ± 4.8	18.6 ± 3.6	20.3 ± 5.1	18.8 ± 4.0
	21.9 ± 9.7	22.3 ± 5.6	24.0 ± 7.1	20.6 ± 4.5
Body fat (%)	30.7 ± 10.7	30.7 ± 7.7	28.3 ± 10.3	26.6 ± 10.5
	28.2 ± 10.9	33.1 ± 10.3	28.9 ± 14.9	25.5 ± 11.5
Fasting insulin (μIU/mL)	15.4 ± 6.3	13.5 ± 11.5	12.8 ± 6.3	10.4 ± 3.8
	15.9 ± 9.7	18.2 ± 9.7	17.5 ± 10.4	11.2 ± 4.5
Insulin sensitivity [×10 ⁻⁴ min ⁻¹ /(μIU/mL)]	4.6 ± 1.6	6.3 ± 3.6	3.7 ± 1.6	6.4 ± 8.0
	3.8 ± 3.1	5.6 ± 4.2	3.2 ± 1.9	8.4 ± 4.8
Tanner Stage 1 (%)	72.7	100	100	100
	21.1	36.4	11.8	64.3
Tanner Stage 2 (%)	18.2	0	0	0
	31.6	36.4	70.6	14.3

Values shown (baseline values in top row) are means ± SD unless indicated as proportions.

dependent outcome can be expressed as e^{β} minus 1). In addition, results revealed a significant three-way interaction among the rate of change in visceral fat, time, and gender ($\beta = -0.04 \pm 0.02, p < 0.01$). In boys, the increase in fasting insulin with every 1-cm² increase in visceral fat per year was not as great as that in girls, with a difference in fasting insulin change of ~4% a year. In other words, gains in visceral fat had a stronger impact on changes in fasting insulin among girls than among boys. There was not a significant interaction between the baseline level of visceral fat and time. Nor were there any statistically significant differences in the relationship between visceral fat and fasting insulin with regard to race or Tanner Stage.

With regard to subcutaneous abdominal fat, a significantly positive relationship was found between the baseline level of subcutaneous abdominal fat and the rate of fasting insulin change ($\beta = 0.002 \pm 0.001, p < 0.02$), after

adjusting for visceral fat and covariates (Table 2). In addition, in children at higher Tanner Stages, compared with those at lower stages, initial subcutaneous abdominal fat had a smaller impact on the rate of change in fasting insulin ($\beta_{\text{initial subcutaneous fat} \times \text{Tanner Stage} \times \text{time}} = -0.001 \pm 0.0003, p < 0.01$). Yet, in children at higher stages, compared with those at lower stages, the rate of subcutaneous abdominal fat change had a greater effect on the rate of change in fasting insulin ($\beta_{\text{initial subcutaneous fat} \times \text{Tanner Stage} \times \text{time}} = 0.003 \pm 0.001, p < 0.01$). There was no significant interaction between the rate of change of subcutaneous abdominal fat and time. Furthermore, no gender or racial differences in the relationship between subcutaneous abdominal fat and fasting insulin were detected.

When predicting fasting insulin with total body fat, we found no significant relationships between either the baseline level or rate of change of total body fat and rate of

Table 2. Separate models predicting the rate of change of fasting insulin from initial and rates of change of visceral fat, subcutaneous abdominal fat, or total body fat

Models	Parameters	Estimates	<i>p</i>
Visceral fat → fasting insulin (adjusting for subcutaneous abdominal fat)	<i>Rate of change of visceral fat × time</i>	0.05 ± 0.03	<0.05
	<i>Rate of change of visceral fat × time × gender</i>	-0.04 ± 0.02	<0.01
	Gender	-0.20 ± 0.09	<0.05
	Subcutaneous abdominal fat	0.002 ± 0.001	<0.05
	Subcutaneous abdominal fat × time	-0.001 ± 0.0003	<0.05
Subcutaneous abdominal fat → fasting insulin (adjusting for visceral fat)	<i>Initial subcutaneous abdominal fat × time</i>	0.002 ± 0.001	<0.02
	<i>Initial subcutaneous abdominal fat × time × Tanner Stage</i>	-0.001 ± 0.0003	<0.01
	<i>Rate of change of subcutaneous abdominal fat × time × Tanner Stage</i>	0.003 ± 0.001	<0.01
	Rate of change of subcutaneous abdominal fat	0.007 ± 0.003	<0.05
	Visceral fat	0.01 ± 0.003	<0.001
	Visceral fat × time	-0.004 ± 0.001	<0.01
	Rate of change of total body fat	0.00007 ± 0.00003	<0.02
Total body fat → fasting insulin (adjusting for lean tissue mass)			

Parameter estimates are regression coefficients ± SE. Fasting insulin was log_e transformed.

Main parameters of interest are indicated in bold italics. Unbolded parameters were covariates.

Main effects represented relations with initial status of fasting insulin.

Gender coded as 1 = boys, 0 = girls. Although only significant terms are shown, all three models adjusted for initial fasting insulin, race, gender, Tanner Stage, baseline age, relevant adipose/lean tissue, and the interactions of these terms with time. Models also adjusted for three-way interactions, specified as 1) the multiplication of (initial independent variable × time) and race, gender, Tanner Stage, respectively, 2) the multiplication of (independent variable slope × time) and race, gender, Tanner Stage, respectively.

fasting insulin change, after adjusting for lean-tissue mass and other covariates (Table 2). There were no differences in the relationship between total body fat and fasting insulin in terms of race, gender, or Tanner Stage. Table 2 also shows the significant covariates in each of the models.

Effects of Fat on the Rate of Change of Insulin Sensitivity

After adjusting for all covariates, we did not find any significant two-way interactions between the baseline level of visceral fat, subcutaneous abdominal fat, or total body fat and the rate of change of insulin sensitivity (*p* > 0.05). Moreover, there were no significant relationships between the rate of change of visceral fat, subcutaneous abdominal fat, or total body fat and the rate of change of insulin sensitivity (*p* > 0.05). There were no significant differences in the relationships between independent fat measures and insulin sensitivity in terms of race, gender, or Tanner Stage. Neither baseline levels nor the rate of accumulation of any of the fat measures predicted changes in insulin sensitivity, regardless of race, gender, or sexual maturation.

Discussion

Our results support the hypothesis that visceral fat was significantly related to fasting insulin but not insulin sensitivity over time, as we have found previously in cross-sectional analysis (7,8). Initial subcutaneous abdominal fat, but not the rate of change of subcutaneous abdominal fat, predicted the rate of change of fasting insulin. In addition, the relationship between subcutaneous abdominal fat and fasting insulin over time may be moderated by the effect of sexual maturation. Total body fat was not significantly related to fasting insulin over time. None of the fat measures were significantly related to the rate of change of insulin sensitivity over time.

With regard to the effect of visceral fat change on change in fasting insulin, our results showed that, independent of subcutaneous abdominal fat, with every 1-cm² increase in visceral fat per year, there was an ~5% increase in fasting insulin per year. Based on our previous work in the same cohort of children, we estimated the growth of visceral fat, independent of subcutaneous abdominal fat, to be ~5.2 cm² a year (9). Given this estimate, we would then expect

the increase in fasting insulin to be $\sim 29.6\%$ per year (i.e., $e^{0.05 \times 5.2}$ minus 1). Thus, independent of the effect of subcutaneous abdominal fat gain, the magnitude of the effect of visceral fat gain on fasting insulin can be considered quite significant. The accumulation of visceral fat, independent of subcutaneous abdominal fat, therefore, may be associated with important disease risks.

Consistent with cross-sectional findings (7,8), visceral fat was found to relate significantly to fasting insulin, but not insulin sensitivity over time. The lack of association between visceral fat and insulin sensitivity in this study may be due to the relatively low accumulation of visceral fat in children. Alternatively, differences between studies may be due to the nature of insulin sensitivity in different subject populations. Whole-body insulin sensitivity reflects both skeletal-muscle glucose uptake and hepatic-glucose production. Differences among subjects in the relative contribution of these two factors to insulin sensitivity may lead to differences in the relationship between insulin sensitivity and visceral fat. In a separate analysis, we found no independent associations between any of the fat compartments and changes in acute insulin response, after adjusting for insulin sensitivity. Therefore, other factors such as insulin clearance or glucose production may be involved.

Initial subcutaneous abdominal fat, rather than the rate of subcutaneous abdominal fat change, predicted fasting insulin change independently of visceral fat, after adjusting for covariates (three-way interactions). Because initial subcutaneous abdominal fat preceded the change in fasting insulin, our finding may render some temporal justification to the causal pathway from subcutaneous abdominal fat to increasing fasting insulin. This stands in contrast to the correlation of visceral fat with fasting insulin, where causality is less evident. Although the magnitude of the effect of subcutaneous abdominal fat was quite small, it is important to note that the accumulation of subcutaneous abdominal fat often outweighs that of visceral fat by several-fold. Therefore, the potential impact of subcutaneous abdominal fat should not be underestimated. Adjusting subcutaneous abdominal fat for total body fat reduced the magnitude of the coefficients (mostly likely due to the high correlation between subcutaneous abdominal fat and total body fat) but did not yield substantially different results.

Total body fat did not seem to predict either change in fasting insulin or change in insulin sensitivity over time. Yet, we have found that cross-sectionally, total body fat was independently associated with insulin sensitivity (7). It is not clear why earlier cross-sectional results were not observed longitudinally in the present analysis. However, at least in adults, it has been argued that abdominal obesity, as opposed to obesity in general, may be more important in predicting risk of type 2 diabetes (10). General adiposity, on the other hand, may be a consequence of lowered insulin

sensitivity and/or hyperinsulinemia rather than a predictor (11) of obesity. Hence, central fat may affect insulin clearance and/or glucose production (12–15), which then stimulates the still-sensitive fat cells in the body to deposit more fat (16–18). Nevertheless, future studies are warranted to further examine the direction of causality.

The lack of association between insulin sensitivity and adiposity is most likely due to the small magnitude of effect insulin sensitivity has on adiposity. The sample size in the current study was relatively small for the complexity of our models. Therefore, power was likely a problem. This may explain why we saw that, cross-sectionally, total body fat or subcutaneous fat was related to insulin sensitivity in prepubertal children, but a similar longitudinal relationship was not observed in the present analysis. We note also that, compared with previous studies published by us and others (e.g., Ref. 7), we have adjusted for many more parameters in the current analysis, and this might have decreased our ability to detect a very small effect of fat on insulin sensitivity. Finally, it could be that the association between fat and insulin sensitivity are stronger after the peak of puberty. Because most of our children were early pubertal during the study, we might not have the appropriate sample to detect this.

Because the current study employed a procedure of convenient sampling, it is limited in its generalization to individuals who do not share characteristics (e.g., race, age, baseline adiposity, etc.) similar to those of our subjects. Specifically, a longer-term study is required to investigate whether the pattern of the associations estimated continues in a similar fashion in late childhood and adolescence, particularly with regard to the linearity and direction of change. Pubertal and postpubertal changes may possibly alter these patterns. Larger samples with repeated measures would also afford the opportunity to detect smaller effects and better examine differences between subgroups of children.

Nevertheless, in spite of the limitations, the current study is the first to estimate the longitudinal, independent relationships between changes in different fat compartments and changes in fasting insulin or insulin sensitivity in a cohort of African-American and white children, using advanced measures of body composition and insulin sensitivity. Increases in visceral fat were found to relate significantly to increases in fasting insulin, independent of changes in subcutaneous abdominal fat. The impact of gains in visceral fat on fasting insulin seemed to be greater in girls than in boys. Initial subcutaneous abdominal fat, but not subcutaneous abdominal fat gain, predicted change in fasting insulin over time independently of visceral fat, rendering temporal support for causality. Growth-related increases in total body fat were not independently predictive of changes in either fasting

insulin or insulin sensitivity, suggesting that abdominal fat may have a greater direct link to elevated fasting insulin but not necessarily insulin sensitivity.

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References

1. **Goran MI, Kaskoun M, Shuman WP.** Intra-abdominal adipose tissue in young children [see comments]. *Int J Obes Relat Metab Disord.* 1995;19:279–83.
2. **Goran MI, Driscoll P, Johnson R, Nagy TR, Hunter G.** Cross-calibration of body-composition techniques against dual-energy X-ray absorptiometry in young children. *Am J Clin Nutr.* 1996;63:299–305.
3. **Pintauro SJ, Nagy TR, Duthie CM, Goran MI.** Cross-calibration of fat and lean measurements by dual-energy X-ray absorptiometry to pig carcass analysis in the pediatric body weight range. *Am J Clin Nutr.* 1996;63:293–8.
4. **Bergman RN, Phillips LS, Cobelli C.** Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest.* 1981;68:1456–67.
5. **Pacini G, Bergman RN.** MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsiveness from the frequently sampled intravenous glucose tolerance test. *Comput Methods Programs Biomed.* 1986;23:113–22.
6. **Yang YJ, Youn JH, Bergman RN.** Modified protocols improve insulin sensitivity estimation using the minimal model. *Am J Physiol.* 1987;253:E595–602.
7. **Gower BA, Nagy TR, Goran MI.** Visceral fat, insulin sensitivity, and lipids in prepubertal children. *Diabetes.* 1999;48:1515–21.
8. **Goran MI, Gower BA.** Longitudinal study on pubertal insulin resistance. *Diabetes.* 2001;50:2444–50.
9. **Huang TT-K, Johnson MS, Figueroa-Colon R, Dwyer JH, Goran MI.** Growth of visceral fat, subcutaneous abdominal fat, and total body fat in children. *Obes Res.* 2001;9:283–9.
10. **Després J-P, Lemieux I, Prud'homme D.** Treatment of obesity: need to focus on high risk abdominally obese patients. *Br J Nutr.* 2001;322:716–20.
11. **Johnson MS, Figueroa-Colon R, Huang TT-K, Dwyer JH, Goran MI.** Longitudinal changes in body fat in African American and Caucasian children: influence of fasting insulin, glucose, and insulin sensitivity. *J Clin Endocrinol and Metab.* 2001;86:3182–7.
12. **Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA.** Effect of fatty acids on glucose production and utilization in man. *J Clin Invest.* 1983;72:1737–47.
13. **Svedberg J, Björntorp P, Smith U, Lonnroth P.** Free-fatty acid inhibition of insulin binding, degradation, and action in isolated rat hepatocytes. *Diabetes.* 1990;39:570–4.
14. **Wiesenthal SR, Sandhu H, McCall RH, et al.** Free fatty acids impair hepatic insulin extraction in vivo [published erratum appears in *Diabetes* 1999;48:1348]. *Diabetes.* 1999;48:766–74.
15. **Hennes MM, Shrago E, Kissebah AH.** Receptor and postreceptor effects of free fatty acids (FFA) on hepatocyte insulin dynamics [see comments]. *Int J Obes.* 1990;14:831–41.
16. **Krssak M, Falk Petersen K, Dresner A, et al.** Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a ¹H NMR spectroscopy study [published errata appear in *Diabetologia* 1999;42:386 and 1999;42:1269]. *Diabetologia.* 1999;42:113–6.
17. **Pan DA, Lillioja S, Kriketos AD, et al.** Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes.* 1997;46:983–8.
18. **Forouhi NG, Jenkinson G, Thomas EL, et al.** Relation of triglyceride stores in skeletal muscle cells to central obesity and insulin sensitivity in European and South Asian men. *Diabetologia.* 1999;42:932–5.