

PAPER

Insulin sensitivity, insulin secretion and β -cell function during puberty in overweight Hispanic children with a family history of type 2 diabetes

GDC Ball¹, MJ Weigensberg², ML Cruz¹, GQ Shaibi³, HA Kobaissi¹ and MI Goran^{1,4*}

¹Department of Preventive Medicine, University of Southern California, Health Sciences Campus, Los Angeles, CA, USA; ²Department of Pediatrics, University of Southern California, Health Sciences Campus, Los Angeles, CA, USA; ³Department of Biokinesiology and Physical Therapy, University of Southern California, Health Sciences Campus, Los Angeles, CA, USA; and ⁴Department of Physiology and Biophysics, University of Southern California, Health Sciences Campus, Los Angeles, CA, USA

OBJECTIVE: To examine cross-sectional differences in insulin sensitivity, insulin secretion and β -cell function during puberty in overweight Hispanic boys and girls with a family history of type 2 diabetes.

STUDY DESIGN AND PARTICIPANTS: This cross-sectional, observational study included 214 8–13-y-old Hispanic children with a BMI percentile \geq 85th percentile and family history of type 2 diabetes.

METHODS AND ANALYSES: Participants underwent a physical examination, body composition measures, oral glucose tolerance test (OGTT), and frequently-sampled intravenous glucose tolerance test. Unadjusted and adjusted general linear models (GLM) tested whether insulin/glucose dynamics differed by Tanner stage and gender.

RESULTS: Unadjusted group comparisons showed that fasting insulin increased whereas insulin sensitivity (SI) and the disposition index (DI) (a measure of pancreatic β -cell function) decreased across Tanner stage groups (all $P < 0.05$). No differences in the acute insulin response to glucose (AIRg), fasting glucose or 2-h glucose were found. After adjusting for covariates, there was no independent effect of Tanner stage on SI ($P = 0.9$) or AIRg ($P = 0.2$), but DI was slightly lower in later Tanner stages suggesting decreased β -cell function in the more mature groups ($P = 0.10$).

CONCLUSIONS: Overweight Hispanic children with a family history of type 2 diabetes may represent a unique population given that pubertal insulin resistance was not evident once analyses controlled for body composition. Longitudinal analyses are required to determine whether the slightly diminished β -cell function in later Tanner stages plays a role in the development of type 2 diabetes.

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Introduction

Several studies have demonstrated that insulin sensitivity (SI, the inverse of insulin resistance) decreases at the onset of puberty.^{1–4} In Caucasian children, decreased SI during puberty is accompanied by increased insulin secretion that normalizes as insulin resistance improves near the end of puberty.⁵ Cross-sectionally, Moran *et al*³ showed that SI (measured using the euglycemic–hyperinsulinemic clamp)

was highest in Tanner stage I, lowest in Tanner stage III (~20% lower than stage I), and near prepubertal levels in Tanner stage V. Using a longitudinal design, Goran and Gower² observed that the pubertal transition from Tanner stage I to III was associated with a 32% reduction in SI (measured by the intravenous glucose tolerance test and minimal modeling) in Caucasian and African–Americans which was consistent across a range of body fatness. Our research group has previously demonstrated that Hispanic and African–American children have lower SI in relation to Caucasians, and while Hispanics compensate for their lower SI by increasing insulin secretion, African–Americans exhibit reduced insulin clearance to help maintain normoglycemia.⁶ Considering the increased prevalence of pediatric overweight in the United States,⁷ changes in insulin action and

*Correspondence: Dr MI Goran, Institute for Prevention Research, Professor of Preventive Medicine and Physiology & Biophysics, Keck School of Medicine, University of Southern California, 1540 Alcazar Street, Room 208–D, Los Angeles, CA 90033, USA.
E-mail: goran@usc.edu

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secretion during maturation may have important implications for children and adolescents in general, and Hispanics specifically, who appear to be at increased risk for developing type 2 diabetes.⁸

Presently, very little data exist regarding the influence of puberty on insulin resistance across all five Tanner stages and, to our knowledge, the impact of puberty on insulin action and secretion in Hispanic children at increased risk of developing type 2 diabetes has not been assessed. Thus, the objective of this investigation was to determine cross-sectional differences in SI, insulin secretion, and β -cell function across all five Tanner stages in a sample of overweight Hispanic children with a family history of type 2 diabetes.

Materials and methods

Participants

Boys and girls were recruited from the greater Los Angeles area. The current analysis included 214 children ($n=123$ boys, $n=91$ girls) enrolled in the University of Southern California Study Of Latino Adolescents at Risk for type 2 diabetes (SOLAR Diabetes Project). Findings from this investigation have been published previously.^{9–13} Participants met the following inclusion criteria at their initial visit: age- and gender-specific BMI ≥ 85 th percentile;¹⁴ Hispanic background (all four grandparents of Hispanic descent); 8–13-y old; family history of type 2 diabetes (sibling, parent, or grandparent) and absence of diabetes evaluated through an oral glucose tolerance test (OGTT).¹⁵ Participants were neither currently taking any medication(s) nor carried a previous clinical diagnosis known to influence body composition, insulin sensitivity, insulin secretion, diet or physical activity. As of spring 2004, all of the children in this longitudinal, observational study had attended at least one of four annual clinic visits; enrollment began in 2001, so some boys and girls had already attended two or three visits. In the present set of analyses, we included data from each child's most recent visit if more than one visit was attended. This was necessary since most of the children were at either Tanner stage I or II at their initial visit. Selecting the most recent visit allowed us to include a greater number of individuals in the more advanced Tanner stages. However, one exception to this approach was required since few children were included in the Tanner stage III group using this technique. Data from children who were rated as Tanner stage III at any one of their annual visits were selected regardless of when that visit occurred. For example, if a child was classified as Tanner stage III at visit one and Tanner stage IV at visit two, visit one data were selected for that child although visit two data were more proximal. No longitudinal analyses were performed at this time and no subjects had data included for more than one visit. Prior to the onset of testing, informed consent and assent were obtained from parents and children, respectively. This investigation was

approved by the Institutional Review Board of the University of Southern California, Health Sciences Campus.

Out-patient visit

Children arrived at the USC General Clinical Research Center (GCRC) at ~0800 hours after an overnight fast. A comprehensive medical history and physical exam including physical maturation was performed by a pediatrician. Tanner stage was assessed by a physician according to the well-established criteria of Marshall and Tanner.^{16,17} Consistent with our earlier reports,^{9–13} Tanner stage was expressed based upon breast development in girls and pubic hair growth in boys, those aspects of pubertal development that reflect the biological activity of gonadal steroid exposure in each sex (testosterone in boys and estrogen in girls). Gonadal steroids were not measured in this study. However, to further validate Tanner stage assignment, we found that pubic hair stage in boys was strongly and positively correlated with testicular volume ($r=0.89$; $P<0.001$) while breast development in girls was strongly and positively associated with pubic hair development ($r=0.84$; $P<0.001$). Nursing staff measured height to the nearest 0.1 cm using a wall-mounted stadiometer and weight to the nearest 0.1 kg using a medical balance-beam scale; body mass index (BMI) was then calculated. A topical anesthetic (EMLA cream, Aztrozeneca LP, Wilmington, DE, USA) was applied to one arm, and at ~0900 hours, a flexible catheter was placed in an antecubital vein. For the OGTT, children ingested 1.75 g of oral glucose solution per kg body weight (to a maximum 75 g) at *time 0*. Blood was sampled and assayed for glucose at -5 min (fasting glucose) and 2 h following the glucose load (2-h glucose). Impaired glucose tolerance (IGT) (2-h glucose: 140–199 mg/dl) and impaired fasting glucose (IFG) (fasting glucose: 100–125 mg/dl) were based on American Diabetes Association criteria.¹⁵

Inpatient visit

At least 7 days after the outpatient visit, children were admitted to the GCRC in the afternoon for an inpatient visit. Subjects underwent a brief physical examination, body composition testing, and a frequently sampled intravenous glucose tolerance test (FSIVGTT).

Body composition. Dual-energy X-ray absorptiometry (DEXA) was used to measure body composition (fat mass and soft lean tissue mass [total lean tissue mass – bone mineral content]) using a Hologic QDR 4500W (Bedford, MA, USA).

Frequently-sampled intravenous glucose tolerance test. Following body composition measurements, subjects were served dinner and an evening snack; all food was consumed prior to 2000 hours. Only water was permitted between 2000 hours and testing the next day. At ~0630

hours the following morning, a topical anesthetic was applied to the antecubital area of both arms and intravenous catheters were inserted into both arms at ~0730 h. Two fasting blood samples were drawn at -15 and -5 min to assess basal insulin and glucose concentrations. At time 0, the FSIVGTT was initiated with glucose (25% dextrose, 0.3 g/kg body weight) administered intravenously over 1 min. Blood samples were collected at 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min. Insulin (0.02 units/kg body weight; Humulin R; Eli Lilly, Indianapolis, IN, USA) was injected intravenously at 20 min. Plasma was analyzed for glucose and insulin concentrations and these values were subsequently entered into the MINMOD MILLENIUM 2003 software program (5.16, R.N. Bergman) for determining SI, acute insulin response to glucose (AIRg), and the disposition index (DI).¹⁸⁻²⁰ SI represents the glucose clearance rate per unit of insulin increase with clearance resulting from either increased peripheral glucose uptake or decrease hepatic glucose production. AIRg reflects the first phase endogenous insulin secretion (within the first 10 min) in response to the glucose infusion, and DI (SI × AIRg) provides an estimate of β-cell function.²¹ Glucose was measured in duplicate using a Yellow Springs Instrument 2700 Analyzer (Yellow Springs Instrument, Yellow Springs, OH, USA) and a glucose oxidase kit. Insulin was assayed in duplicate using a specific human insulin enzyme-linked immunosorbent assay kit (Linco, St Charles, MO, USA).

Statistics. Weight, BMI, fat mass, soft lean tissue mass, fasting insulin, 2-h glucose, SI, AIRg, and DI were not normally distributed, so these variables were log transformed prior to further analyses. Unadjusted group differences in age, height, log weight, log BMI, BMI percentile, log fat mass, log soft lean tissue mass, log fasting insulin, fasting glucose, log 2-h glucose, log SI, log AIRg, and log DI were determined using five (Tanner stage: I-V) × 2 (gender: boy, girl) general

linear models (GLM). Gender was included as a fixed factor along with Tanner stage since previous research has shown that girls may have lower SI than boys.^{3,22} Subsequently, adjusted 5 × 2 GLM for log fasting insulin, fasting glucose, log 2-h glucose, log SI, log AIRg, and log DI were run after covarying age, fat mass, and soft lean tissue mass; SI was also included as a covariate when AIRg was entered as the dependent variable. Unadjusted and adjusted models were followed up with pair-wise contrasts using a Bonferroni correction for multiple comparisons. χ^2 tests were used to assess differences across Tanner stages for dichotomous variables including IGT, IFG, and gender. Statistics were conducted with SPSS (11.0, 2001, SPSS Inc, Chicago, IL, USA) with *a priori* significance set at $P < 0.05$.

Results

Unadjusted group comparisons for anthropometric and body composition variables according to Tanner stage and gender are presented in Table 1. Except for BMI percentile, variables tended to increase across increasing Tanner stage groups. However, Tanner stage II and III groups were similar in weight, BMI, fat mass, and soft lean tissue mass and stages IV and V were not significantly different in any variable. There were more boys in the early Tanner stages and more girls in the later Tanner stages ($\chi^2 = 36.3$, $P < 0.001$). Overall, boys were older (estimated marginal means ± s.d.) (12.5 ± 1.4 vs 11.4 ± 1.1 y), taller (158.6 ± 9.7 vs 149.6 ± 7.8 cm), heavier (75.3 ± 20.4 vs 66.5 ± 16.4 kg) and had greater soft lean tissue mass (46.2 ± 9.6 vs 36.9 ± 7.7 kg) than girls (all $P < 0.05$).

Unadjusted analyses showed that fasting insulin tended to increase while SI and DI tended to decrease across increasing Tanner stages; no main effect of Tanner stage was found for fasting glucose, 2-h glucose or AIRg (Table 1). Boys had higher fasting glucose than girls ($P = 0.003$), but gender differences were not observed for any of the other variables.

Table 1 Comparison of anthropometric, body composition, and insulin/glucose variables across tanner stages (unadjusted mean ± s.d.)

	Tanner I (n = 63)	Tanner II (n = 59)	Tanner III (n = 28)	Tanner IV (n = 36)	Tanner V (n = 28)	Main effects**
Boys/girls (n/n)	50/13	41/18	12/16	11/25	9/19	Tanner
Age (y)	10.3 ± 1.2 ^a	11.4 ± 1.5 ^b	11.9 ± 1.4 ^c	13.1 ± 1.0 ^d	13.4 ± 0.9 ^d	Tanner, gender
Height (cm)	143.6 ± 9.2 ^a	151.0 ± 9.6 ^b	153.7 ± 7.6 ^c	160.6 ± 7.3 ^d	162.9 ± 7.3 ^d	Tanner, gender
Weight (kg)*	56.8 ± 15.4 ^a	67.6 ± 18.6 ^b	67.4 ± 14.9 ^b	81.8 ± 16.7 ^c	85.6 ± 16.7 ^c	Tanner, gender
BMI (kg/m ²)*	27.1 ± 5.0 ^a	29.2 ± 5.1 ^{ab}	28.4 ± 5.1 ^{ab}	31.6 ± 5.3 ^b	32.1 ± 4.8 ^b	Tanner
BMI percentile	97.2 ± 3.2	97.8 ± 2.5	96.2 ± 3.9	97.4 ± 3.3	98.0 ± 1.7	NS
Fat mass (kg)*	22.5 ± 8.5 ^a	27.0 ± 9.4 ^b	26.9 ± 9.8 ^b	31.1 ± 10.1 ^{bc}	31.0 ± 10.5 ^{bc}	Tanner
Soft lean tissue mass (kg)*	32.0 ± 7.2 ^a	38.5 ± 9.8 ^b	39.6 ± 7.9 ^b	47.2 ± 8.6 ^c	50.6 ± 9.3 ^c	Tanner, gender
Fasting insulin (μU/ml)*	16.1 ± 9.7 ^a	21.5 ± 9.8 ^{ab}	20.1 ± 12.4 ^{ab}	23.8 ± 14.1 ^b	23.1 ± 9.8 ^{ab}	Tanner
Fasting glucose (mg/dl)	91.4 ± 6.5	91.3 ± 5.3	92.8 ± 5.7	91.0 ± 6.9	91.6 ± 7.6	Gender
2-h glucose (mg/dl)*	124.4 ± 15.9	129.0 ± 17.8	121.6 ± 13.2	128.6 ± 22.2	129.6 ± 20.1	NS
SI* (× 10 ⁻⁴ min ⁻¹ /μU/ml)	2.44 ± 1.76 ^a	1.75 ± 0.97 ^{ab}	1.87 ± 1.11 ^{ab}	1.36 ± 0.74 ^b	1.38 ± 0.99 ^b	Tanner
AIRg* (μU/ml)	1762 ± 1274	1877 ± 1080	1829 ± 1417	1798 ± 1372	1576 ± 1137	NS
DI* (× 10 ⁻⁴ min ⁻¹)	2996 ± 1504 ^a	2601 ± 1133 ^a	2213 ± 893 ^{ab}	1895 ± 857 ^b	1646 ± 885 ^b	Tanner

*Variable was log transformed prior to analysis; nonlog-transformed values are presented for ease of interpretation. **Results of two-way general linear model; significant main effects ($P < 0.05$) of Tanner stage and gender are shown. SI, insulin sensitivity; AIRg, acute insulin response to glucose; DI, disposition index. Values with different superscript letters across columns are significantly different from one another ($P < 0.05$).

Neither IGT ($\chi^2 = 5.0$, $P = 0.3$) nor IFG status ($\chi^2 = 1.7$, $P = 0.8$) differed by Tanner stage. The results that follow included all children, regardless of glucose tolerance status, since our findings did not differ when participants with IGT or IFG were excluded (data not shown).

Adjusted analyses revealed no significant main effect of Tanner stage for fasting insulin, fasting glucose, 2-h glucose, SI, or AIRg although a trend suggested lower DI ($P = 0.10$) across increasing Tanner stage groups after adjusting for age, fat mass, and soft lean tissue mass. Group comparisons in SI, AIRg, and DI according to Tanner stage and gender are presented in Figure 1a–c, respectively. We also found that fat mass was positively related to fasting insulin ($P < 0.001$) and negatively associated with SI ($P < 0.001$) and DI ($P = 0.04$). In addition, SI was inversely related to AIRg ($P < 0.001$). Boys had higher fasting glucose levels than girls (93.8 ± 10.5 vs 90.3 ± 6.8 mg/dl, $P = 0.01$), but no other gender effects emerged. We did not observe any significant Tanner stage-gender interactions.

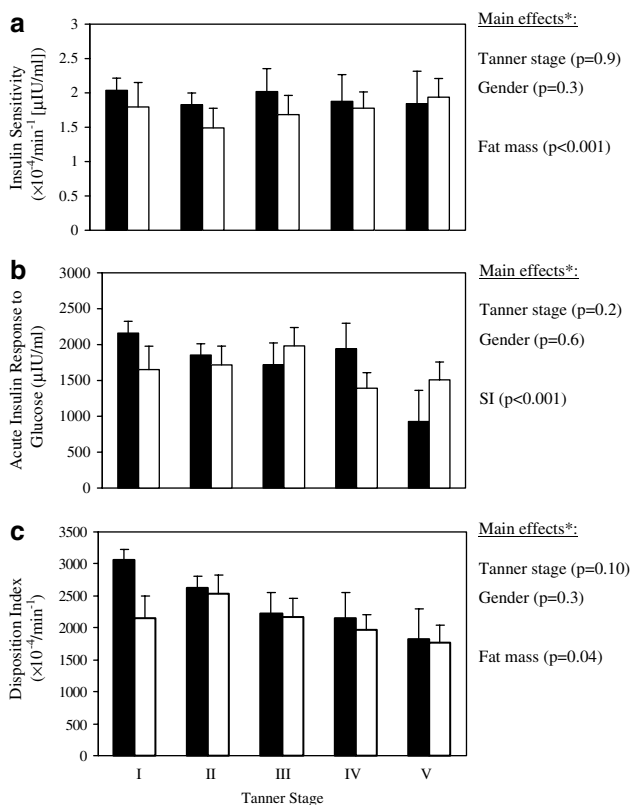


Figure 1 Comparison of (a) insulin sensitivity (SI), (b) acute insulin response, (AIRg) and (c) disposition index (DI) according to Tanner stage and gender adjusted for age, fat mass, soft lean tissue mass, and SI (SI entered as covariate for AIRg only) (estimated marginal means \pm s.e.). Figure shows that main effect of Tanner stage was not significant for SI or AIRg, but a trend suggested slightly lower DI in the more advanced Tanner stage groups. Black bars (boys), white bars (girls). *Analyses performed using log-transformed data; nonlog-transformed values are presented for ease of interpretation. Insulin conversion: ($\mu\text{IU}/\text{ml} \times 6.945 = \text{pmol}/\text{l}$).

Discussion

Numerous studies have evaluated the impact of puberty on insulin resistance,^{1,2,4,5,22,23} but to our knowledge, this represents the first investigation in overweight Hispanic youth. This research examines a critical issue since the effects of puberty on insulin dynamics in the Hispanic population may play a role in their increased risk of developing type 2 diabetes early in life. Our objective was to compare SI, insulin secretion, and β -cell function, across puberty in overweight Hispanic boys and girls with a family history of type 2 diabetes. In unadjusted analyses, fasting insulin tended to increase while SI and DI tended to decrease across increasing Tanner stage groups. After adjusting for body composition, there was no independent effect of Tanner stage on SI or insulin secretion, but a trend showed marginally lower β -cell function in later Tanner stages. These findings indicate that overweight Hispanic children with a family history of type 2 diabetes may represent a unique group in which a fall in SI during puberty is not evident. The independent effect of puberty on insulin resistance appears to be masked by the high level of body fat and (possibly) the positive family history of type 2 diabetes. The slightly decreased β -cell function in later Tanner stages suggests that the increased risk of type 2 diabetes in this group may be a function of deteriorating β -cell compensation, although longitudinal analyses are required to confirm this observation.

Body fat

We have previously demonstrated using a longitudinal design that SI decreased ($\sim 33\%$) in Caucasian and African-American children as they progressed from Tanner stage I to III and that this drop in SI was similar in children at low, medium, and high levels of body fat.² We are unable to make direct comparisons between our two studies given differences in ethnic groups and methodologies, but in the present investigation, controlling for fat mass rendered the effect of Tanner stage nonsignificant which highlights the critical role that body fat plays in moderating SI in overweight Hispanic youth. Although these data are cross-sectional, the prominent effect of fat is underscored by the fact that SI was $\sim 38\%$ lower in the Tanner stage III group vs Tanner stage I group in the unadjusted analysis; however, between group differences were reduced to $\sim 4\%$ after controlling for adiposity in covariate analysis. It is possible that a threshold exists at which point SI may not decrease any further, but it would seem that children in this sample have not yet reached such a level given that SI decreased across increasing Tanner stage groups in the unadjusted analyses. We lack a leaner group of children for comparison, but it is likely that this sample of overweight Hispanic children would be considered very insulin resistant in relation to a nonoverweight group. Our data do not generally agree with previous reports of pubertal insulin

resistance, but we submit that others have not examined such a unique high-risk population.

Family history of type 2 diabetes

SI and β -cell function are impaired in nondiabetic adults with first-degree relatives who have type 2 diabetes indicating that a family history of type 2 diabetes increases diabetes risk.^{24,25} Positive family history of type 2 diabetes in both mothers and fathers may increase the risk of type 2 diabetes in offspring, but it appears that the maternal influence is strongest.²⁶ In Arizona Pima Indians, *in utero* exposure to diabetes was responsible for ~40% of type 2 diabetes in children and adolescents and >70% in young adults.²⁷ In mothers, both genetic heritability and/or fetal exposure to excess metabolic fuels (ie, glucose and amino acids) *in utero* can influence offspring pancreatic β -cell growth, development and function which can impair insulin action and/or secretion later in life.²⁸ We have previously shown that a family history of type 2 diabetes, as well as the degree of family history, failed to explain differences in risk of type 2 diabetes in a sample of Caucasian, African-American and Hispanic children (Tanner stages I and II; $n = 21$ matched pairs).²⁹ The somewhat lower β -cell function in the more mature Tanner stages within the present study are consistent with data suggesting that diabetes risk may not manifest until adolescence or young adulthood.^{27,30} Most studies of pubertal insulin resistance have not reported family history of type 2 diabetes^{3,4,23,31} and a control group without a family history of type 2 diabetes is not available to us for comparison purposes. However, in the context of other known risk factors (ie, overweight, Hispanic ethnicity), the positive family history of type 2 diabetes may have reduced our ability to detect subtle differences in SI or insulin secretion across Tanner stage groups.

Insulin secretion and β -cell function

Considering that SI did not vary by Tanner stage in the adjusted analyses, it was not surprising that AIRg did not differ across groups either. In the unadjusted analyses, DI differed by Tanner stage with the Tanner stage V group being lower (42% in boys; 34% in girls) than in the Tanner stage I group. However, the main effect of Tanner stage was diminished after adjusting for age and body composition, with fat mass also a significant correlate of DI. These data provide suggestive evidence that β -cell function may decrease in advanced Tanner stage groups and that this deterioration may also be a function of fat mass.

Previous reports have shown that type 2 diabetes is more common in adolescents vs children.³² The progressive loss of β -cell function is thought to precede the development of IGT and type 2 diabetes³³ and DI is an important feature distinguishing overweight Hispanic youth with and without IGT.¹² Longitudinal analyses will be required for supportive evidence, but if SI remains low in these children as they

mature (a likely scenario given their high fat mass), insulin secretion must remain elevated to help maintain normoglycemia. Over time, the increased secretory demands associated with prolonged insulin resistance may not be sustainable. Therefore, if β -cell compensation deteriorates, an occurrence that could be enhanced through genetic predisposition and/or *in utero* programming via gestational diabetes, decreased metabolic control and type 2 diabetes may be more likely in susceptible individuals. In addition, it is important to appreciate that other factors are known to play key roles in determining β -cell function. Approximately, 25% of the variability in DI appears to be related to genetic factors^{34,35} and specific fat depots (ie, intrahepatic) may be intimately related to β -cell function,³⁶ so additional research in these areas is warranted.

Limitations

Including data from the baseline visit for all participants would have been a logical sampling approach for these analyses, but would have left us with very few children in the mid-Tanner stages and none at stage V. Although we purposefully selected children in the Tanner stage III group, we believe that this had a negligible impact on the results given the observational nature of this study in which objective and accurate measurements were performed. We included *visit number* as a covariate (in addition to the other covariates) in the GLM models, but this had no bearing on our findings (data not shown). We acknowledge that these findings are probably not generalizable to other populations given the elevated risk of type 2 diabetes of this sample. Therefore, we cannot presume that Tanner stage does not independently influence SI in youth who are nonoverweight, possess higher SI, or lack a positive family history of type 2 diabetes. Insulin-like growth factor 1 and growth hormone concentrations increase transiently during puberty³⁷ and are believed to play a prominent role in puberty-associated insulin resistance,³⁸ so the inclusion of these variables may have been useful in data interpretation. Cross-sectional data for this study were derived from a cohort of overweight Hispanic children participating in a longitudinal study to explore risk factors for the development of type 2 diabetes. Although a control group would have been useful from a comparison standpoint, this was not possible given the study design. Finally, cause-and-effect relationships cannot be made given the cross-sectional study design, but follow-up longitudinal analyses will be performed as this cohort progresses through puberty.

Summary

In this sample of overweight Hispanic youth with a family history of type 2 diabetes, SI and secretion did not differ across Tanner stage groups although a trend revealed that β -cell function was marginally lower in more advanced Tanner stage groups after adjusting for covariates. Although

previous reports have shown that SI decreases and insulin secretion increases concomitantly during puberty, the high degree of body fat and positive family history of type 2 diabetes in this overweight Hispanic group may have overwhelmed the independent impact of puberty on insulin resistance. Longitudinal studies are required to examine if the lack of overt pubertal insulin resistance in this sample has any physiological effects and whether lower β -cell function in later Tanner stages precedes the development of type 2 diabetes in this high-risk group.

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