Sex Hormone–Binding Globulin and Testosterone in Individuals With Childhood Diabetes

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OBJECTIVE — Insulin downregulates hepatic production of sex hormone–binding globulin (SHBG), which in turn influences sex hormone bioavailability. The effects of childhood-onset diabetes and insulin resistance in nondiabetic individuals on SHBG and testosterone in children and young adults are poorly understood.

RESEARCH DESIGN AND METHODS — Individuals with diabetes diagnosed at <18 years of age ($n = 48$) and their siblings without diabetes ($n = 47$) were recruited for the Chicago Childhood Diabetes Registry Family Study. SHBG and total and free testosterone were measured. Participants ranged in age from 10 to 32 years; 39% were non-Hispanic white. The majority of individuals with diabetes had the classic type 1 phenotype (75%), while the remainder exhibited features of type 2 or mixed diabetes; 96% were treated with insulin.

RESULTS — SHBG and total testosterone were higher in male subjects with diabetes compared with those in male siblings. Elevated SHBG was associated with the absence of endogenous insulin independent of sex; elevated total testosterone was similarly associated with the absence of C-peptide for male subjects only. Diabetes type and treatment were unrelated. In those without diabetes, greater insulin resistance had a small, nonsignificant association with lower SHBG and higher free testosterone.

CONCLUSIONS — SHBG and total testosterone appear to be higher in male children and young adults with diabetes compared with nondiabetic male siblings, which is apparently related to the absence of endogenous insulin. This may have implications for sex hormone–dependent processes across the lifespan in male individuals diagnosed with diabetes as children.

Diabetes Care **31:1207–1213, 2008**

Previous research has demonstrated that hepatic production of sex hormone–binding globulin (SHBG) is downregulated by insulin (1). SHBG, in turn, influences the relative balance and bioavailability of testosterone and estradiol (2). Conditions associated with altered systemic insulin levels such as type 1 diabetes and insulin resistance in nondiabetic individuals could therefore affect SHBG and sex hormones and their dependent physiological processes. For example, changes in bioavailable estradiol and testosterone levels may partly explain such factors as the delayed age at menarche (3) demonstrated in girls with type 1 diabetes. Understanding these associations may therefore have clinical implications.

Previous research evaluating the association of type 1 diabetes with SHBG has produced conflicting results demonstrating lower (children), similar (children and premenopausal women), and higher (postmenopausal women and adult men) levels in those with type 1 diabetes than in control subjects (4–8). Research on testosterone in male subjects with type 1 diabetes has consistently found elevated levels compared with those in control subjects (6), whereas studies in female subjects (children and adults) have been inconsistent, demonstrating comparable to higher levels of testosterone (4,7,8). Results regarding the effect of glycemic control (4,5,8) and insulin treatment (5,6) on sex hormones in type 1 diabetes have also been equivocal. However, these studies used small samples ($n < 100$) without adjustment for potential confounders such as age and body composition, and all were limited to non-Hispanic whites.

Among individuals without diabetes, fasting insulin and insulin resistance are negatively associated with SHBG in both adult men and women (9,10). The associations of fasting insulin and insulin resistance with testosterone are negative in nondiabetic men (10) but positive in nondiabetic women (11). There have been no similar studies in children and adolescents without diabetes.

Therefore, we sought to understand whether altered sex hormones occur in those with childhood diabetes across the spectrum of demographic characteristics after adjustment for important confounders and whether insulin is associated with sex hormones in children without diabetes. Based on the insulin-SHBG relationship, we hypothesized that SHBG is higher in those with diabetes than in sibling control subjects and is related to absent endogenous insulin production, irrespective of diabetes type or treatment, and that insulin resistance is associated with lower SHBG in siblings without diabetes. Based on previous studies in type 1 diabetes, we hypothesized that testosterone levels are higher in those with childhood diabetes than in control subjects.

RESEARCH DESIGN AND METHODS

— The Chicago Childhood Diabetes Registry Family Study is an ongoing study of the epidemiology of diabetes in an ethnically diverse sample. Individuals with diabetes were invited to participate if they were aged <18 years at diagnosis, their diabetes was not secondary to another medical condition, and they were currently living in the Chicago

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Received for publication 13 November 2007 and accepted in revised form 12 March 2008.
Published ahead of print at http://care.diabetesjournals.org on 17 March 2008. DOI: 10.2337/dc07-2169.
Abbreviations: HOMA, homeostasis model assessment; SHBG, sex hormone–binding globulin.

area. Recruitment occurred through diabetes clinics, health fairs, and mailings. All biological first- and second-degree relatives were also invited to participate. Currently, 66 individuals with diabetes (probands) and their families have completed the examinations. The subsample for this analysis includes 48 probands and 47 full and half siblings without diabetes who were ≥10 years of age and therefore had sex hormone determinations. Probands and siblings from the same family, probands without siblings, and siblings without probands meeting these criteria were all included in the analysis. None of the female subjects reported current use of hormonal contraceptives. Examinations were conducted in the University of Chicago's General Clinical Research Center or participants' homes. Study approval was obtained from the University of Chicago's institutional review board. Participants aged ≥18 years and parents of children aged <18 years provided written informed consent; children aged 10–17 years assented.

Data collection and variables

SHBG and testosterone (dependent variables). Plasma SHBG and total and free testosterone were determined from a fasting sample irrespective of menstrual phase because they vary little over the cycle. SHBG was measured with an assay standardized to the dialysis technique (12). Total and free testosterone was determined by a solid-phase ^{125}I radioimmunoassay (Siemens Medical Solutions Diagnostics, Los Angeles, CA). SHBG and testosterone were measured by the University of Chicago's endocrinology laboratory. The lower limits of detection for total and free testosterone were 10 ng/dl (0.3 nmol/l) and 2 pg/ml (6.9 pmol/l), respectively. Intra-assay coefficients of variation (CVs) were ≤10%.

Diabetes characteristics (independent variables). Diabetes status was the main predictor. Type of diabetes treatment (insulin, pills, both, or diet only), frequency of insulin injections, and disease duration were determined via questionnaire. Participants who reported using ≥3 insulin injections per day or an insulin pump were considered on intensive treatment. Participants were classified as type 1 diabetic (16 male and 20 female) if they *1*) had no detectable C-peptide or *2*) had detectable C-peptide with <2 years diabetes duration and were either positive for islet autoantibodies (GAD and insulinoma-associated protein 2 [IA2]) or receiving intensive insulin monotherapy. Participants were classified as type 2 diabetic (four male and four female) if they *1*) had detectable C-peptide and no antibodies or *2*) among those who were missing data on antibodies, had detectable C-peptide and used oral antidiabetic medication, received no treatment, or discontinued using insulin ≥2 years after diagnosis without severe complications, or had diabetes duration ≥2 years. Those classified as mixed phenotype (three male and one female) had detectable C-peptide and autoantibodies, with ≥2 years diabetes duration.

Additional blood measurements (independent variables). Fasting C-peptide, insulin, and glucose were also determined. Individuals with diabetes with a fasting blood glucose <150 mg/dl (8.3 mmol/l) had a stimulated C-peptide measurement 90 min after ingestion of a 6 ml/kg standard nutrient solution (Boost; Novartis Nutrition, Minneapolis, MN). Plasma C-peptide was measured with a solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic Products, Los Angeles, CA) in the University of Chicago's Diabetes Research and Training Center lab. The lower limit of detection was 0.17 nmol/l, and the intra-assay CV was 8%. Absent C-peptide was defined as a fasting and stimulated level below the detection limit. Serum insulin was measured with a solid-phase, two-site chemiluminescent immunometric assay (Immulite 1000; Siemens Medical Solutions Diagnostics, Los Angeles, CA) by the Diabetes Research and Training Center lab. The intra-assay CVs were ≤8.0%. Fasting glucose was measured with a glucometer (One Touch Sure Step; Lifescan, Milpitas, CA). Using fasting insulin and glucose, insulin resistance was determined in nondiabetic siblings by the homeostasis model assessment (HOMA), version 2.0 (13). Insulin resistance was defined as a value ≥3.2 for those aged ≤18 years (14) and ≥2.5 for those aged >18 years (15).

A1C was measured in whole venous blood with a monoclonal antibody method (DCA 2000; Bayer, Elkhart, IN). The detection range was 2.5–14.0%, and the intra-assay CVs were ≤5%.

Adjustment variables. Height was measured without shoes using a stadiometer rod, and weight and percent body fat were measured with subjects barefoot with a bioelectrical impedance analyzer scale (Tanita TBF-300A; Tanita, Arlington Heights, IL). BMI was transformed into *Z* scores using the Centers for Disease Control and Prevention Growth Chart (for ages ≤20 years) (16) and National Health and Nutrition Examination Survey (NHANES) III (for ages >20 years) (17) age- and sex-matched reference data. Waist circumference was measured twice at the umbilical level and averaged. Other potential confounders included age at exam, sex, and race/ethnicity. Race/ethnicity was defined as that reported for three or more grandparents; if less than three grandparents shared the same race/ethnicity, race was considered mixed. When race/ethnicity was available on less than three grandparents, race/ethnicity was based on parental data. If parental data were missing, self-reported race/ethnicity was used. Pubertal stage was self-assessed with pubic hair Tanner diagrams. For 18 participants, pubertal stage was imputed using age-, sex-, and race-specific estimates (18). Female subjects self-reported age at menarche.

Statistical analyses

Probands and siblings were first compared using unadjusted mixed linear and logistic regression models, with family entered as a random effect to incorporate correlation due to clustering within families. Effects of diabetes status on SHBG and on total and free testosterone were then evaluated using multivariable mixed linear regression, again with family entered as a random effect. All multivariable models adjusted for pubertal stage and race/ethnicity. Potential confounders explored were body composition (BMI *Z* score, percent body fat, or waist circumference), age at exam, diabetes treatment, and diabetes type; a covariate was retained in the model if it produced at least a 10% change in the diabetes status regression parameter. If more than one body composition variable met the criterion for confounding, the variable that produced the largest change was included. Interactions of diabetes status by sex were tested, and stratified models were fit when significant.

Analyses were performed for subgroups to examine effects of covariates applicable only to that subgroup (probands: disease duration, age at diagnosis, diabetes type, treatment, number of insulin injections per day, and intensive insulin therapy; siblings: HOMA2 and fasting insulin) or subgroups whose covariate effects were expected to differ by diabetes status (fasting C-peptide, A1C, or glu-

Table 1—*Characteristics by diabetes status*

Characteristic	Probands with diabetes	Siblings without diabetes
n	48	47
Age at exam (years)	17.1 ± 5.7	15.4 ± 3.7
Tanner stage (pubic hair) (%)		
1	4.2	14.9
2	8.3	6.4
3	18.7	8.5
4	31.3	29.8
5	37.5	40.4
Sex (%)		
Female	52.1	40.4
Male	47.9	59.6
Race/ethnicity (%)		
Non-Hispanic white	33.3	44.7
Non-Hispanic black	39.5	23.4
Other	6.3	10.6
Mixed	14.6	14.9
Mexican Hispanic	6.3	6.4
Anthropometrics		
BMI *Z* score*	0.8 ± 0.9	0.4 ± 1.2
Body fat (%)	27.5 ± 10.0†	22.3 ± 11.7
Waist circumference (cm)	78.7 ± 13.7	74.0 ± 13.4
Blood measurements		
Fasting glucose (mg/dl)	199.8 ± 101.2‡	90.1 ± 6.9
A1C (%)	8.6 ± 2.0‡	5.1 ± 0.3
Fasting C-peptide (nmol/l)	0.3 ± 0.4‡	0.7 ± 0.4
Absent C-peptide (%)	66.7	
Diabetes duration (years)	7.7 ± 6.1	
Age at diagnosis (years)	9.4 ± 3.7	
Diabetes treatment (%)		
Insulin only	91.6	
Insulin and pills	4.2	
Pills only	4.2	
Insulin therapy (%)§		
1–2 injections/day	41.3	
3–4 injections/day	37.0	
Pump	21.7	
Diabetes type (%)‖		
Type 1 diabetes	75.0	
Type 2 diabetes	16.7	
Mixed	8.3	
Insulin resistance		
Fasting insulin (μU/ml)		9.5 ± 10.1
HOMA2 (using fasting insulin)		1.2 ± 1.2
Insulin resistant (%)¶		4.3

Data are means ± SD or percent. To convert milligrams per deciliter to millimole per liter for glucose, multiply by 0.055; to convert microunits per milliliter to picomole per liter for insulin, multiply by 6.0. *BMI was transformed into *Z* scores using the Centers for Disease Control and Prevention Growth Chart (age ≤20 years) and National Health and Nutrition Examination Survey (NHANES) III (age >20 years) age- and sex-matched reference data. †$P < 0.05$. ‡$P < 0.0001$. §Subgroup using insulin, $n = 46$. ‖Diabetes type based on C-peptide levels, presence of diabetes antibodies, diabetes treatment, symptoms while off of insulin, and duration. ¶Insulin resistant criteria based on fasting insulin HOMA2: *1*) if age ≤18 years, insulin resistance defined as HOMA2 ≥3.2 and *2*) if age >18 years, insulin resistance defined as HOMA2 ≥2.5.

cose). Models limited to probands included only one individual per family; thus, linear rather than mixed linear regression models were fit. Interactions with sex were tested for each covariate.

Sensitivity analyses were conducted by limiting the final models to individuals with type 1 diabetes or those receiving insulin treatment. Models excluding the 18 individuals with imputed puberty data were also analyzed. Results did not change substantially and are therefore presented using the entire sample.

Statistical tests were considered significant at $P < 0.05$. Mixed linear regression analyses were performed using SAS, version 8.0 (SAS Institute, Cary, NC) and mixed logistic regression using Stata/SE 9.2 (StataCorp LP, College Station, TX).

RESULTS — Age of participants ranged from 10 to 32 years; 39% were non-Hispanic white (Table 1). Among female subjects, 77% had begun menstruating at an average age of 12.6 years. Characteristics of probands and siblings were similar except that probands had significantly higher percent body fat, A1C, and fasting glucose and lower fasting C-peptide. Among probands, mean disease duration was 7.7 years (range 0.4–28.5) and current A1C was 8.6%. All male subjects were treated with only insulin; two female subjects were treated with insulin plus pills, and two female subjects were treated with pills only. Of the insulin users, 59% were on an intensive insulin regimen. All siblings without diabetes fell within the normal range for A1C (<6%), and two siblings met the criteria for insulin resistance.

The effect of diabetes status on SHBG differed between male and female subjects ($P = 0.008$; Fig. 1*A*). Among male subjects, SHBG was significantly higher in probands than in siblings across pubertal stage (mean difference [Δ] 9.5 nmol/l [95% CI 2.8–16.1]), adjusting for body composition and race. Higher levels were demonstrated in male subjects both with type 1 (10.9 nmol/l [3.2–18.6]) and type 2 (10.3 nmol/l [−2.4 to 23.0]) diabetes. This association was not observed in female subjects (3.0 nmol/l [−5.2 to 11.3]). Among siblings, female subjects had higher SHBG than male subjects, whereas SHBG did not differ by sex among probands. SHBG was highest in Tanner stages 1–2 with lower levels during later puberty. SHBG did not differ by race/ethnicity.

In male subjects, total testosterone differed significantly by diabetes status (Fig. 1*B*). In contrast, total and free testosterone in female subjects was uniformly low with virtually no difference across diabetes status (Fig. 1*B* and *C*). Specifically,

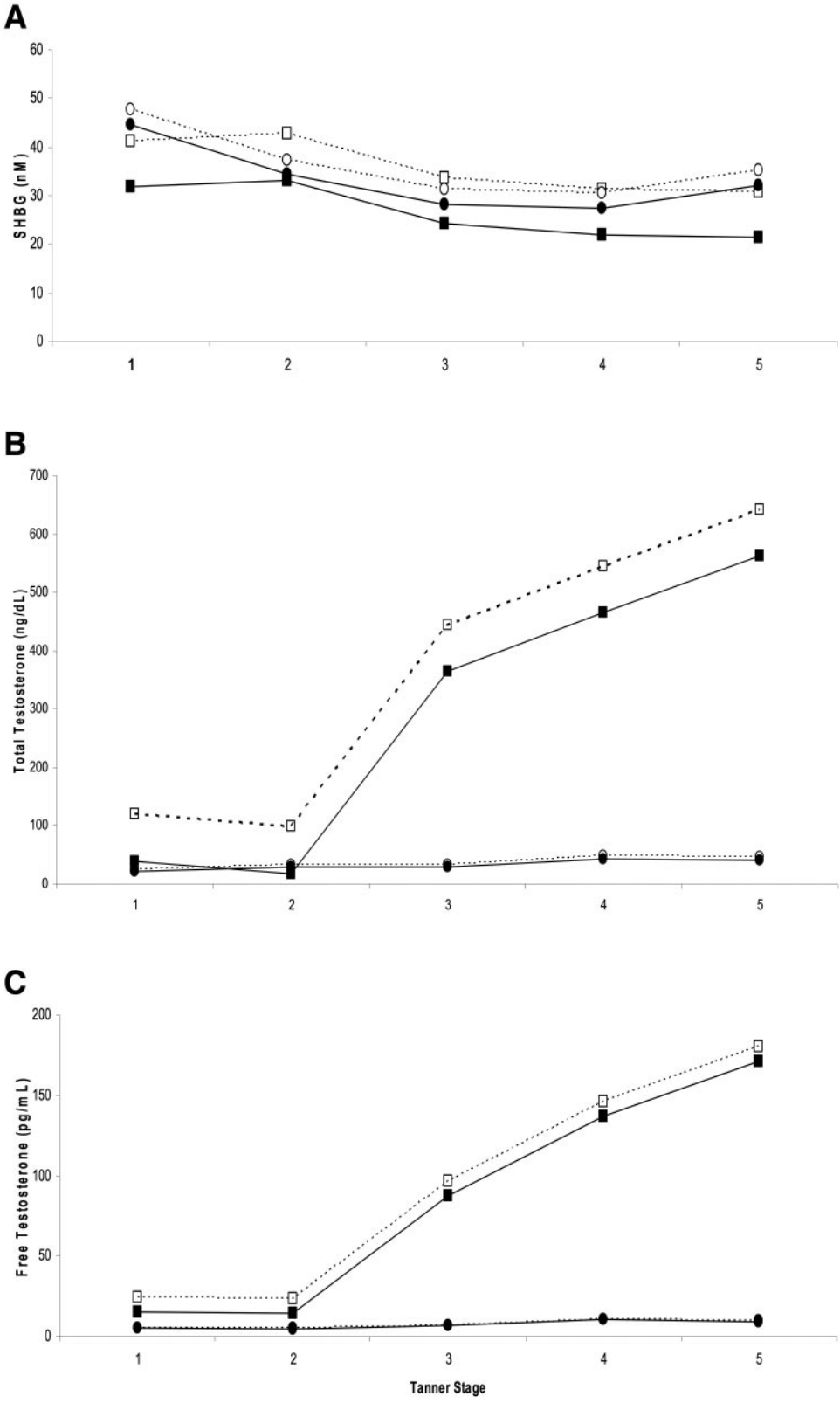

Figure 1—*Mean sex hormone levels by childhood diabetes status for male and female subjects across Tanner stages 1–5* (n = *9, 7, 13, 29, and 37, respectively). Levels adjusted for body composition and race. Solid lines with black symbols, siblings without diabetes* (n = *47); dashed lines with white symbols, probands with diabetes* (n = *48; 36 with type 1 diabetes, 8 with type 2 diabetes, and 4 with mixed phenotype); squares, male subjects* (n = *51); circles, female subjects* (n = *44). A: SHBG, significant interaction between diabetes status and sex.* B*: Total testosterone, significant interaction between diabetes status and sex (to convert nanogram per deciliter to nanomole per liter, multiply by 0.03467).* C*: Free testosterone (to convert picogram per milliliter to picomole per liter, multiply by 3.467).*

male subjects with diabetes had significantly higher total testosterone than those without diabetes (Δ 80.4 ng/dl [2.8 nmol/l]) (95% CI 0.1–160.7), adjusting for body composition and race. Higher levels were found in male subjects both with type 1 (106.4 ng/dl [3.7 nmol/l]) (4.4–208.4) and type 2 (75.7 ng/dl [2.6 nmol/l]) (−103.4 to 254.7) diabetes. A difference was not observed in female subjects (5.1 ng/dl [0.2 nmol/l]) (−8.5 to 18.8) (interaction $P = 0.01$). Testosterone did not differ by race/ethnicity.

In final models adjusted for sex, pubertal stage, body composition, and race, higher SHBG in probands was associated with absent versus detectable C-peptide levels (Δ 7.6 nmol/l [95% CI 2.1–13.0]) and also with longer diabetes duration (years) (0.7 nmol/l [0.2–1.2]). These associations did not differ by sex. In male but not female subjects, the lack of C-peptide was also significantly associated with higher total testosterone (male subjects: Δ152.6 ng/dl [5.3 nmol/l] [95% CI 26.2–279.0]; female subjects: 24.7 ng/dl [0.9 nmol/l] [−106.7 to 156.0]). SHBG and total testosterone were not significantly associated with age at diagnosis, A1C, fasting glucose, diabetes type or treatment, or number of insulin injections per day or intensive insulin therapy. There were no significant associations with free testosterone.

In the combined group of male and female siblings without diabetes, adjusting for sex, pubertal stage, body composition, and race, SHBG and testosterone were not significantly associated with fasting C-peptide, A1C, glucose, or insulin. Although SHBG and free testosterone levels were not significantly associated with HOMA2, weak trends were observed. A 1-unit increase in HOMA2 was associated with a −4.6 nmol/l (95% CI −11.0 to 1.9) ($P = 0.15$) decrease in SHBG and a 23.5 pg/ml [81.5 pmol/l] (−6.2 to 53.3) ($P = 0.12$) increase in free testosterone. HOMA2 was not significantly related to total testosterone ($P = 0.43$). None of these associations differed by sex.

CONCLUSIONS — To our knowledge, this study is the first to show that among male individuals, SHBG and total testosterone are higher in children and young adults with diabetes than in nondiabetic siblings, even after adjustment for relevant confounders. Among female subjects, SHBG was slightly higher in those with diabetes than in nondiabetic siblings, but the difference was not significant. Total testosterone in female subjects also showed no association with diabetes status. Furthermore, we demonstrated not only that the absence of endogenous insulin as measured by C-peptide was significantly associated with elevated SHBG and, in males, with total testosterone but also that higher SHBG was positively related to disease duration.

Prior research in children and adolescents with type 1 diabetes (aged ~6–20 years) has been inconsistent, demonstrating lower, similar, and slightly elevated SHBG compared with that in control subjects (5,7) even though each study controlled for pubertal status. These contradictory findings may be due to the small and/or select clinical samples examined. The results of this study suggest that prior conflicting reports may also be a function of the lack of adjustment for body composition, a failure to account for sex differences, and/or heterogeneity in C-peptide status and diabetes duration. In contrast, results by diabetes status in adults have been more consistent. SHBG has been demonstrated to be similar in premenopausal women (aged ~20–55 years) with and without type 1 diabetes (8), whereas significantly higher SHBG has been found in middle-aged men (aged ~20–55 years) (6) and postmenopausal women (aged ~50–70 years) (4) with type 1 diabetes.

Prior research on testosterone by diabetes status has also produced divergent results by sex. In male subjects, studies have consistently found elevated testosterone in individuals with type 1 diabetes compared with that in control subjects (6,7). Studies in female subjects have demonstrated less coherence, with similar or elevated testosterone in both children (7) and adults (4,8) with type 1 diabetes compared with that in control subjects. These inconsistent results in female subjects could again be due to small samples. However, one key reason for the contradictory results in female subjects may be a lack of adjustment for body composition, as adiposity is strongly related to testosterone (19).

Within the context of the previous literature, this study demonstrates that male subjects diagnosed with diabetes in childhood have significantly elevated SHBG and testosterone versus male subjects without diabetes. In contrast, among female subjects with childhood diabetes, any alterations in sex hormones are small, suggesting sex differences in the effect of diabetes on sex hormone physiology.

The associations of higher SHBG and total testosterone with diabetes among male subjects reported here are consistent with free testosterone levels that do not differ by diabetes status and echo previous studies in adult male subjects (6). This lack of association results from the high affinity with which SHBG binds to testosterone to influence its bioavailability (2). In addition to varying by diabetes status, SHBG and testosterone exhibited the predicted changes across pubertal stage, irrespective of diabetes. Also, consistent with known sex differences in nondiabetics, female subjects had higher SHBG than male subjects (2).

Elevated SHBG in male and female subjects and total testosterone in male subjects were strongly associated with the absence of C-peptide in those with diabetes, regardless of phenotype. This is consistent with the upregulation of hepatic SHBG production in response to low insulin levels (1). Thus, higher SHBG in those with childhood diabetes may reflect hepatic hypoinsulinemia despite peripheral hyperinsulinemia from exogenous treatment (6). The relationship of absent endogenous insulin with elevated testosterone in male individuals with childhood diabetes is likely more complicated, as insulin has been shown to stimulate gonadal testosterone production in individuals without diabetes (20). Perhaps peripheral hyperinsulinemia associated with insulin treatment (which increases with decreasing C-peptide) (6) has a greater effect on gonadal testosterone production than does portal insulin level. However, we did not find an association between testosterone and intensive insulin therapy. A more precise measure of exogenous insulin exposure may be needed to determine whether insulin treatment mediates the relationship between absent C-peptide and elevated testosterone. Unfortunately, those data were not available in this study. Disease duration was also positively associated with SHBG. However, neither SHBG nor testosterone was associated with A1C, fasting glucose, or type or intensity of treatment. These results indicate that sex hormones in those with childhood-onset diabetes may be more strongly affected by the long-term absence of portal insulin and the clinical course of diabetes than by short-term, more modifiable factors such as glycemia.

Compared with male nondiabetic subjects, male subjects with both type 1 and type 2 childhood diabetes had eleva-

tions in SHBG and testosterone of similar magnitudes; the comparisons with type 2 diabetic subjects were not significant likely due to limited power. In contrast, previous research has shown that adult male individuals with type 2 diabetes have lower SHBG and testosterone compared with control subjects (21). One explanation for these conflicting results could be that male subjects categorized as having type 2 diabetes in our sample may actually have type 1 diabetes. However, even though they were diagnosed before age 18 years and used insulin, all were antibody negative and had detectable C-peptide after ≥5 years duration. Thus, type 2 diabetes appearing in childhood may well differ from adult type 2 diabetes in its association with sex hormones. For example, prospective research indicates that low SHBG and testosterone are risk factors for type 2 diabetes in older men (i.e., sex hormones affect diabetes risk) (21). In contrast, alterations in sex hormones by childhood type 2 diabetes may be more akin to childhood type 1 diabetes (i.e., diabetes characteristics such as endogenous insulin affect sex hormones). This is consistent with research demonstrating that diabetes in children represents a spectrum combining various levels of β-cell dysfunction with insulin resistance rather than two distinct phenotypes (22). Studies using larger samples of children with non–type 1 diabetes are needed to confirm these results.

The sex differences in absolute levels of sex hormones by diabetes status detected in our and other studies may be due to sex differences in biologic processes linking diabetes and sex hormone production. For example, sex differences may exist in the associations of SHBG and total testosterone with C-peptide and disease duration, even though our study had limited power to detect this. Research must continue to explore the potential reasons for sex differences in the relationship between childhood diabetes and sex hormone physiology.

In the siblings without diabetes, insulin resistance tended toward a negative association with SHBG and a positive association with free testosterone, although neither reached statistical significance. The magnitude of the decrease in SHBG for a 1-unit increase in HOMA2 was approximately one-half the difference attributable to diabetes status in male subjects and, therefore, has clinical relevance. The trend with SHBG, although weak, is consistent with research in both male and female adults without diabetes, demonstrating insulin resistance to be negatively associated with SHBG (9,10). In comparison, previous research in nondiabetic adults has found testosterone to be lower in male and higher in female subjects with insulin resistance (10,11). In our study, the lack of a statistically significant association between insulin resistance and SHBG and the interaction between insulin resistance and sex on testosterone may be due to the low values and limited variability in insulin resistance in this group of relatively young, healthy siblings, as only two met criteria for insulin resistance. It may also be due to the imprecision of using a single fasting serum insulin level and thus one HOMA value (1).

The current study was cross-sectional, limiting conclusions on how sex hormones change with age in individuals with childhood diabetes; however, these individuals appear to follow a pattern consistent with age differences in individuals without diabetes. This study was also underpowered to detect subtle differences in SHBG and testosterone by diabetes type, sex differences in the associations of C-peptide with SHBG and testosterone in those with diabetes, and associations of insulin resistance with SHBG and free testosterone in siblings without diabetes. Finally, data on insulin dose were not available to fully explore whether insulin therapy mediated the association between C-peptide and testosterone. Yet, the research had a number of strengths, including the ethnically diverse sample. Using sibling controls and measuring and adjusting for potential confounders (especially body composition) also minimized genetic and lifestyle differences between those with and without diabetes to better estimate the effect of diabetes. To our knowledge, this is the first study to examine the association of insulin resistance with sex hormones in children and young adults without diabetes.

Alterations in SHBG have important physiological relevance for sex hormones. High SHBG lowers the proportion of sex hormone available by binding estradiol and testosterone and influences the relative balance of estradiol to testosterone through bidirectional feedback (2). These alterations may then affect sex hormone–dependent processes. It is possible that the changes detected in the sex hormone milieu in children and young adults with diabetes are not modifiable and may only be averted by preventing the disease in the first place. However, sex hormone abnormalities in young people without diabetes may perhaps be avoided by preventing insulin resistance.

In summary, SHBG and total testosterone appear to be significantly higher in male children and young adults with diabetes, which is apparently a function of the absence of endogenous insulin. Whether insulin resistance and SHBG are associated in young people without diabetes calls for further research. Both associations may have implications for sex hormone–dependent processes across lifespan.

Acknowledgments— This research was supported by National Institutes of Health grants DK44752 and RR00055.

Parts of this study were presented in abstract form at the 67th annual meeting of the American Diabetes Association, Chicago, IL, 22–26 June 2007.

We gratefully acknowledge the study participants and the staff of the Chicago Childhood Diabetes Registry Family Study, particularly Latrisha Hampton and Carmela Estrada.

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