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Impaired Insulin Secretion in the Turner Metabolic Syndrome

VLADIMIR K. BAKALOV, MARGARET M. COOLEY, MICHAEL J. QUON, MEI LIN LUO, JACK A. YANOVSKI, LAWRENCE M. NELSON, GAIL SULLIVAN, AND CAROLYN A. BONDY

Developmental Endocrinology Branch (V.K.B., M.M.C., M.L.L., J.A.Y., L.M.N., C.A.B.), National Institute of Child Health and Human Development, and National Center for Complementary Medicine (M.J.Q., G.S.), National Institutes of Health, Bethesda, Maryland 20892

An increased prevalence of impaired glucose homeostasis (IGH) and diabetes mellitus is reported in monosomy X, or Turner syndrome (TS). To determine whether IGH is an intrinsic feature of this syndrome, independent of obesity or hypogonadism, we compared results of a standard oral glucose challenge in age- and body mass index-matched women with TS and with karyotypically normal premature ovarian failure (POF). Fasting glucose levels were normal in both groups, but glucose values after oral glucose challenge were higher in TS [2-h glucose, 135 ± 36 mg/dl (7.5 ± 2.0 mmol/liter) in TS and 97 ± 18 mg/dl (5.4 ± 1.0 mmol/liter) in POF; $P < 0.0001$]. Glucose-stimulated insulin secretion was lower in TS; *e.g.* the initial insulin response ($\Delta I/\Delta G_{30}$) was decreased by 60% compared with POF ($P < 0.0001$). We also compared responses to a standard iv glucose tolerance test in women with TS and in age- and body mass index-matched normal women and found that the insulin area under the curve was 50% lower in women with TS ($P = 0.003$). Insulin sensitivity measured by the quantitative insulin sensitivity check index was higher in women with TS compared with both control groups. Thus, IGH is not secondary to obesity or hypogonadism in TS, but it is a distinct entity characterized by decreased insulin secretion, suggesting that haploinsufficiency for X-chromosome gene(s) impairs β-cell function and predisposes to diabetes mellitus in TS. (*J Clin Endocrinol Metab* 89: 3516–3520, 2004)

TURNER SYNDROME (TS) is caused by partial or total monosomy X. Its two most constant features are short stature, attributed to haploinsufficiency for the homeodomain transcription factor encoded by *SHOX* (1, 2), and gonadal dysgenesis, for which the genetic cause is less clear. An increased prevalence of both type 1 and type 2 diabetes mellitus is also reported in TS (3). A number of studies have reported impaired glucose homeostasis (IGH) in children (4, 5) as well as adults (6–8), with one study suggesting that insulin resistance may be the primary defect in the Turner metabolic phenotype (9). A limiting factor in all these studies, however, has been the absence of control groups matched for body mass or gonadal status. Women with TS tend to have increased adiposity compared with age-matched controls (8, 10, 11), and their hypogonadism and/or hormone replacement therapy may have additional confounding effects in studies of glucose homeostasis. The goal of the present study was to compare glucose homeostasis in women with TS, in age- and body mass index (BMI)-matched women with spontaneous, karyotypically normal premature ovarian failure (POF), and in normal healthy female controls. Thus, by controlling for these potentially confounding variables, we hoped to clarify whether IGH is an intrinsic feature of TS, independent of adiposity and/or hypogonadism, thereby implicating X-chromosome gene(s) in glucose homeostasis, and if so, whether insulin resistance or β-cell dysfunction is the primary mechanism.

Abbreviations: BMI, Body mass index; CV, coefficient of variation; IGH, impaired glucose homeostasis; IVGTT, iv glucose tolerance test; OGTT, oral glucose tolerance test; POF, premature ovarian failure; TS, Turner syndrome.

Subjects and Methods

Study subjects

Women with TS and 46,XX POF were recruited mainly through notices posted on internet web sites. Normal healthy women volunteers were recruited through the National Institutes of Health (NIH) Patient Recruitment Office. Subjects were informed of the nature of the studies and signed informed consents that were approved by the National Institute of Child Health Institutional Review Board. Karyotype analysis of G-banded chromosomes in 50 peripheral blood cells was performed for women with TS and POF. Diagnosis of TS was based on X-monosomy or X-deletion affecting ≥ 70% of lymphocytes and the presence of short stature and ovarian failure. Diagnosis of POF was based on finding at least 4 months of amenorrhea, two determinations of FSH levels greater than 40 mIU/ml, and a normal 46,XX karyotype. Women with a prior history of diabetes mellitus or use of medications known to affect carbohydrate metabolism were excluded from the study. All study subjects discontinued ovarian hormone treatment at least 2 wk before the study and were in good general health and were euthyroid as determined by physical examination and screening lab tests.

Oral glucose tolerance test (OGTT)

Study subjects were placed on a carbohydrate-replete diet (300 g/d) for 3 d before inpatient testing at the NIH Clinical Center. They fasted overnight and received 1.75 g/kg oral dextrose (maximum, 75 g) in the morning. Blood was sampled for glucose and insulin before and at 30, 60, 120, and 180 min after the administration of the dextrose. Glucose homeostasis was examined in women with POF during 1997–1999, at which time, insulin was measured by RIA (Covance, Vienna, VA). The range of normal fasting values for this assay was 2–21 μIU/ml (14–144 pmol/liter), with a mean of 11 μIU/ml (79 pmol/liter). The intraassay coefficient of variation (CV) was 10.9% at a level of 7.5 μIU/ml (54 pmol/liter) and 4.2% at a level of 17 μIU/ml (123 pmol/liter). The

interassay CV was 10% for values near 12 μIU/ml (85 pmol/liter) and 8.5% for values near 45 μIU/ml (324 pmol/liter). Glucose homeostasis was examined in women with TS during 2000–2002 when the Covance insulin RIA had been discontinued, and insulin was measured by a comparable immunochemiluminescent assay (Immulite 2000 analyzer; Diagnostic Products Corporation, Los Angeles, CA). Reference fasting values for this assay are 6-27 μIU/ml [43–194 pmol/liter; mean, 16 μIU/ml (115 pmol/liter)]; the intraassay CV was 5% and the interassay CV was 7.5% at 24 μIU/ml (172 pmol/liter). To allow comparisons across the two assays, insulin values are expressed as Z scores in the following way: (measured insulin − mean value for the assay)/SD of the assay. Glucose was measured by the glucose oxidase method on an LX-20 Beckman Coulter Analyzer (Beckman Coulter, Inc., Fullerton, CA) for all studies.

Intravenous glucose tolerance test (IVGTT)

To further study insulin secretion, we performed IVGTT in women with TS and age-matched healthy women recruited through the volunteer office of NIH during 2001–2003. IVGTT was performed in the morning after an overnight fast with the study subject in a recumbent position. One antecubital vein on each arm was cannulated, and 0.3 g/kg dextrose as 20% water solution was injected over 45 sec in one of the veins. Blood was drawn from the contralateral antecubital vein at −5, −1, 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 20 min for measuring of serum insulin and glucose concentration. Glucose was measured as noted earlier, and insulin was measured by an immunochemiluminescent assay, as described earlier.

Statistics

Data are expressed as mean ± SE bars (figures), mean ± SD (tables and text), or as percentages. Differences between group means were examined by analysis of covariance with Fisher's protected least significant difference procedure. Differences of the mean insulin and glucose levels at the different time points of the OGTT and IVGTT were examined by multivariate analysis of covariance. Comparisons of proportions were made by the Z test with Yates correction. Correlations were examined by Pearson's product. The significance level was set at $P = 0.05$. StatView 5.01 (SAS Institute, Cary, NC) was used for all analyses.

Results

All women with POF had a normal 46,XX karyotype. The spectrum of karyotypes in women with TS was similar to that reported in larger studies (3). Estradiol levels were very low in the two groups [27.8 ± 7.9 pg/ml (102 ± 29 pmol/liter) for TS *vs.* 27.5 ± 7.6 pg/ml (101 ± 28 pmol/liter) for POF], which were also well matched for age and BMI (Table 1). The prevalence of a family history (first-degree relative) of diabetes mellitus was also similar in the two groups (seven of 25 subjects in the TS group and eight of 33 subjects in the POF group; $P = 0.73$).

OGTT

Fasting glucose levels were slightly lower but glucose levels after the oral glucose load were significantly higher in women with TS, with the mean 2-h glucose more than 50% higher than in POF controls (Table 1 and Fig. 1). Nine (36%) of 25 women with TS compared with zero of 33 women with POF demonstrated impaired glucose homeostasis as defined by a 2-h glucose of more than 140 mg/dl (7.8 mmol/liter; $P < 0.001$) (Table 1). Three women with TS (12%) had a 2-h glucose of more than 200 mg/dl (11.1 mmol/liter), suggesting a tentative diagnosis of diabetes mellitus by World Health Organization criteria. Measures of insulin secretion, including the homeostasis model of assessment-β, which reflects basal conditions (12), the early insulin response to glucose (13), and first phase insulin release (14) were all significantly reduced in the TS group (Table 1 and Fig. 1). Insulin sensitivity measured by the quantitative insulin sensitivity check index (15) was higher in women with TS (0.40 ± 0.04) compared with women with POF (0.34 ± 0.02; $P < 0.001$).

Even the women with TS who had normal glucose homeostasis [2-h glucose ≤ 140 mg/dl (7.8 mmol/liter)] demonstrated significantly lower insulin responses than women with POF (Fig. 2 and Table 2), suggesting that impaired insulin release is a very early defect in the Turner metabolic syndrome, which is apparently compensated by enhanced insulin sensitivity. The glucose tolerance seems to worsen with age, as seen in Table 2.

IVGTT

To further investigate insulin secretion in TS, we compared responses to an IVGTT in women with TS *vs.* age- and BMI-matched healthy female volunteers. Insulin release was markedly lower in women with TS, especially during the earliest time points (Fig. 3 and Table 3). As observed, compared with women with POF, insulin sensitivity measured by the quantitative insulin sensitivity check index was better in women with TS compared with normal controls. Acute

TABLE 1. Response to an OGTT in women with TS and POF

	TS (n = 25)	POF (n = 33)	*P*
Age (yr)	30 ± 9	33 ± 4	0.13
BMI (kg/m^2)	22 ± 2	22 ± 2	0.92
Fasting plasma glucose (mmol/liter)	4.5 ± 0.4	4.7 ± 0.3	0.01
Glucose AUC (mmol·liter^{-1}·180)	1339 ± 269	1042 ± 148	<0.0001
2-h glucose (mmol·liter)	7.5 ± 2.0	5.4 ± 1.0	<0.0001
Impaired glucose homeostasis (n, %)	9 (36)	0	0.0004
Insulin secretion			
HOMA-β	118 ± 81	178 ± 57	0.0001
I-AUC$_{180}$ (Z score)	720 ± 446	1310 ± 647	0.0002
I-AUC$_{30}$ (Z score)	50 ± 103	151 ± 103	0.0002
ΔI/ΔG$_{30}$ (Z score·mmol^{-1}·liter)	1.97 ± 1.80	5.0 ± 4.40	<0.0001
First phase insulin release (pmol)	766 ± 562	1302 ± 447	<0.0001

Data are expressed as mean ± SD.

To convert glucose concentration to mg/dl, divide concentration in mmol/liter by 0.0555; to convert insulin concentration to μIU/ml, divide concentration in pmol/liter by 7.175.

AUC, Area under the curve; HOMA, homeostasis model of assessment; I-AUC, insulin area under the curve; ΔI, change in insulin; ΔG, change in glucose.

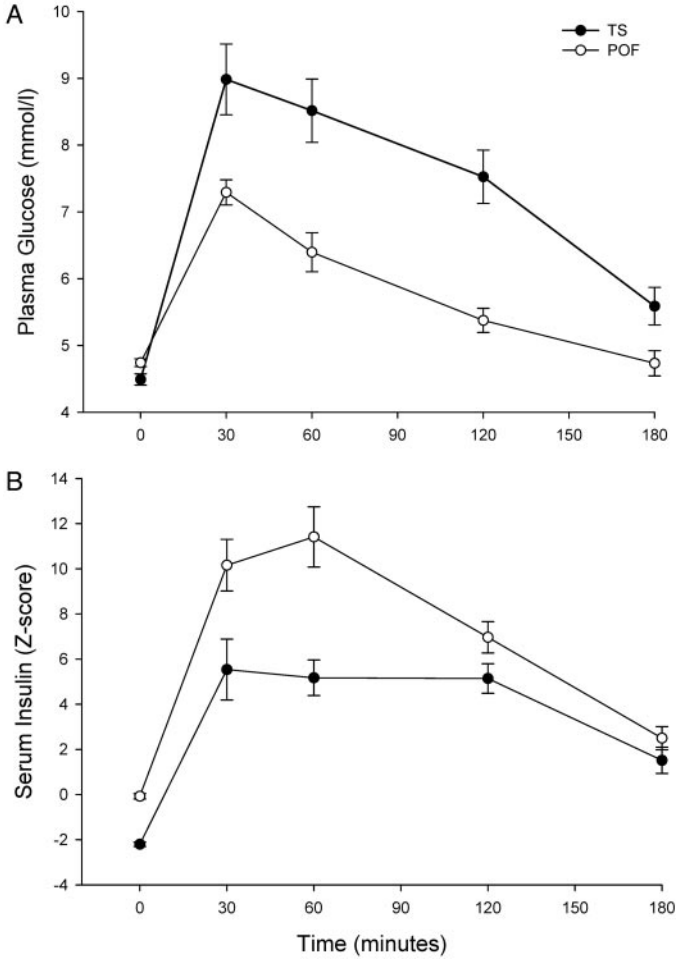

FIG. 1. Glucose (A) and insulin (B) responses to OGTT in women with TS and POF. Except for time zero, all glucose levels were significantly higher in women with TS compared with women with POF ($P < 0.05$). At all time points except 180 min, women with TS had significantly lower insulin Z scores compared with women with POF ($P < 0.05$). To convert glucose concentration to mg/dl, divide concentration in mmol/liter by 0.0555.

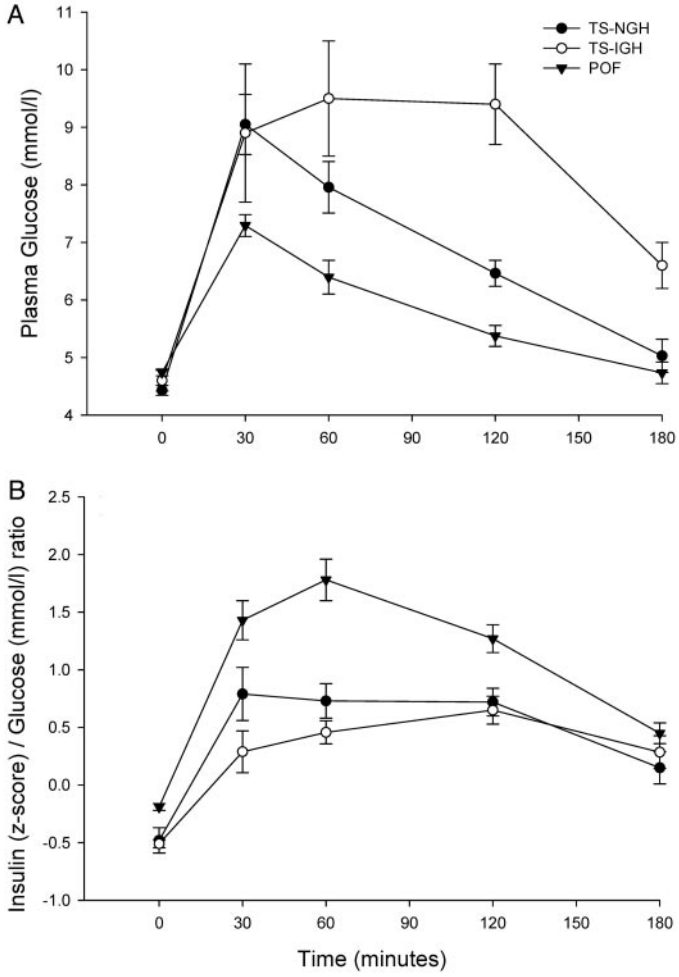

FIG. 2. Glucose (A) and insulin (B) responses to OGTT in women with TS subdivided into groups with normal glucose homeostasis (NGH) and IGH [TS-IGH: all with 2-h glucose > 140 mg/dl (7.8 mmol/liter)], compared with women with POF. Women with TS and NGH had significantly higher ($P < 0.05$) blood glucose levels at 30, 60, and 120 min compared with women with POF. The insulin Z scores were significantly reduced in women with TS-NGH compared with women with POF at 30, 60, and 120 min ($P < 0.05$). To convert glucose concentration to mg/dl, divide concentration in mmol/liter by 0.0555.

insulin response appears to decrease significantly with age in women with TS ($r = -0.303$, $P = 0.035$, Pearson correlation) but not in normal controls ($r = 0.12$, $P = 0.30$). This is also evident from Table 2, in which glucose tolerance and insulin release are progressively impaired with increasing age.

Discussion

This study has shown that women with TS demonstrate reduced glucose-stimulated insulin release compared with age- and BMI-matched women with 46,XX POF and compared with normal cycling women. We realize that this finding should be interpreted with caution in view of the different assays used to measure insulin in the TS group and the POF group, despite the fact that we made an effort to minimize the possible assay bias by converting the absolute insulin concentrations to Z scores. This insulin deficiency in TS is more pronounced in older women with IGH but is apparent even in younger women with normal glucose homeostasis. The fact that reduced insulin secretion is evident in young, nonobese women with perfectly normal insulin sensitivity suggests that β-cell dysfunction or insufficiency is a primary feature of the Turner metabolic syndrome. The reduction in β-cell function appears to be compensated to some extent by enhanced insulin sensitivity in younger women, but as insulin secretion and sensitivity decline with advancing age, IGH and diabetes mellitus may evolve in many individuals with TS. This pathogenetic profile is reminiscent of mature-onset diabetes of the young syndromes caused by haploinsufficiency for transcription factors involved in β-cell survival or function (16, 17). Similar to our observations in TS, individuals with mutations in *HNF1a* or *HNF4* demonstrate reduced insulin secretion and IGH to glucose challenge associated with normal or enhanced insulin sensitivity (18, 19), and it appears that some mutation carriers maintain glucose tolerance for many years due to this enhanced insulin sensitivity. By analogy with these well-

TABLE 2. IGH *vs.* NGH in TS

	TS according to 2-h OGTT glucose			*P*	
	DM ≥11.1 mmol/liter (n = 3)	IGH 7.8–11 mmol/liter (n = 6)	NGH <7.8 mmol/liter (n = 16)	DM *vs.* NGH	DM *vs.* IGH
Age (yr)	39 ± 3	34 ± 10	27 ± 2[a]	0.002	0.26
BMI (kg/m^2)	21.6 ± 2.8	21.3 ± 2.1	22.3 ± 1.9	0.57	0.82
Fasting glucose (mmol/liter)	5.0 ± 0.8	4.4 ± 0.16	4.4 ± 0.34	0.01	0.01
HOMA-β	67 ± 41	108 ± 93	132 ± 82[a]	0.14	0.39
QUICKI	0.40 ± 0.04	0.40 ± 0.03	0.39 ± 0.04[c]	0.75	0.72
Glucose AUC_{180} (mmol·liter^{-1}·180)	1860 ± 330	1358 ± 154	1235 ± 165	<0.0001	<0.0001
I-AUC_{30} (Z score)	2285 ± 1335	4502 ± 1841	6375 ± 4427[c]	0.12	0.20
$\Delta I/\Delta G_{30}$ (Z score·mmol^{-1}·liter^{-1})	0.79 ± 0.51	1.97 ± 1.45	2.19 ± 2.03[a]	0.53	0.90
First phase insulin release (pmol)	242 ± 547	734 ± 480	877 ± 566[b]	0.044	0.16

DM, Diabetes mellitus; NGH, normal glucose homeostasis; HOMA, homeostasis model of assessment; QUICKI, quantitative insulin sensitivity check index; AUC, area under the curve; I-AUC, insulin area under the curve; ΔI, change in insulin; ΔG, change in glucose.

To convert glucose concentration to mg/dl, divide concentration in mmol/liter by 0.0555.

TS-NGH *vs.* POF: [a] $P < 0.01$; [b] $P < 0.001$; [c] $P < 0.0001$.

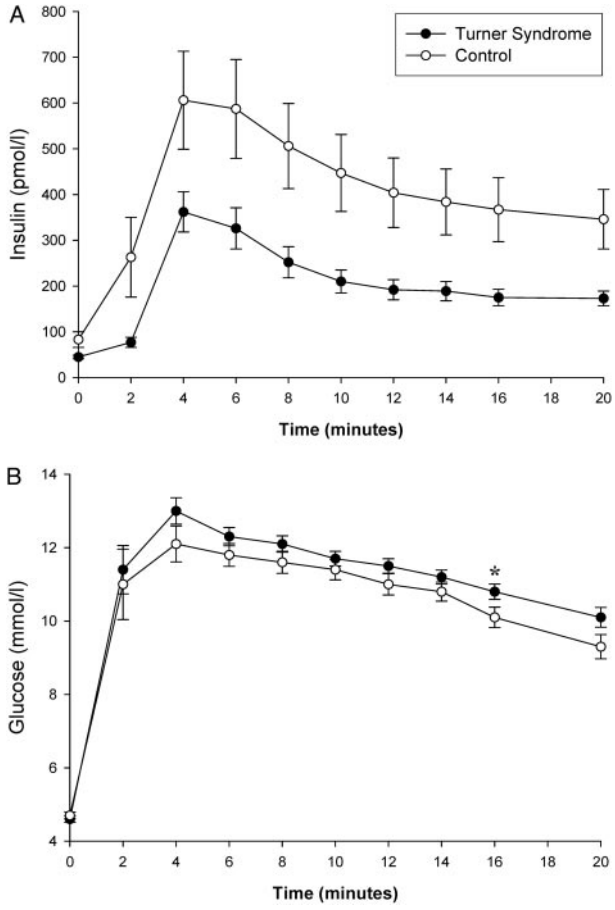

FIG. 3. Insulin (A) and glucose (B) responses during IVGTT in women with TS and sex-, age-, and BMI-matched controls. Women with TS had statistically lower serum insulin levels during all time points (A) on the IVGTT (multivariate ANOVA, *t* test). *, $P < 0.05$. To convert glucose concentration to mg/dl, divide concentration in mmol/liter by 0.0555. To convert insulin concentration to μIU/ml, divide concentration in pmol/liter by 7.175.

described syndromes, we suggest that haploinsufficiency for unknown X-chromosome gene(s) may be responsible for impaired β-cell function in TS.

There is a syndrome of immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance caused by mutations of *FOXP3*, which encodes a forkhead transcription factor apparently involved in immune function (20). This usually fatal disorder manifests full-blown, type 1diabetes in infancy. This is obviously not the typical phenotype in TS, and we have not found evidence for islet cell autoimmunity or association between IGH and autoimmune hypothyroidism in TS (our unpublished data). However, there is a long history of more subtle observations connecting the X-chromosome and diabetes risk. A male preponderance of type 1 diabetes among Caucasians in the United States, United Kingdom, and Sardinia has been linked to Xp (21), and a recent European study suggests that the male excess in diabetes diagnosed in adults is neither specific for the immune-mediated form nor is it human leukocyte antigen-DQ restricted (22). An X-linked diabetes gene would explain the male preponderance and the opposite sex bias in parental transmission of diabetes mellitus because affected fathers would never transmit the trait to sons, whereas affected mothers would be more likely to produce affected sons than daughters.

A Danish registry study reported an approximately 10-fold increase in insulin-dependent diabetes mellitus (defined by the use of insulin) and an approximately 4-fold increase in noninsulin-dependent diabetes mellitus in TS (3). Most investigators familiar with TS, however, do not find any excess of typical early-onset, immune-mediated type 1 diabetes (8, 23). In our experience with about 150 subjects with TS, we have not encountered any such cases. Thus, it seems likely that the increased prevalence of insulin-dependent diabetes mellitus reported in the Danish study may reflect the insulinopenia described in this report and a likely marked insulin-responsiveness in TS. A euglycemic insulin clamp study found that peripheral insulin sensitivity was reduced by 20–25% in girls with TS compared with controls (9). In that small study, however, controls were not matched for BMI, gender, pubertal status, or insulin level during the clamp, so it seems possible that a confounder such as excess adiposity may explain altered glucose disposal rates in these girls. A recent study using a frequently sampled IVGTT with minimal model assessment found that insulin sensitivity was similar in Danish adults with TS compared with age- and

TABLE 3. Insulin and glucose responses to the IVGTT in women with TS and normal healthy female controls

	TS (n = 49)	Control (n = 33)	*P*	*P*[a]
Age (yr)	35 ± 11	37 ± 11	0.31	
BMI (kg/m^2)	27 ± 6	29 ± 9	0.15	
Fasting glucose (mmol/liter)	4.6 ± 0.6	4.7 ± 0.5	0.62	0.86
Fasting insulin (pmol/liter)	45 ± 24	83 ± 98	0.004	0.03
QUICKI	0.379 ± 0.035	0.359 ± 0.042	0.005	0.09
G-AUC (mmol·liter^{-1}·20 min)	223 ± 31	212 ± 38	0.10	0.01
I-AUC (pmol·liter^{-1}·20 min)	4143 ± 3212	8326 ± 8908	0.001	0.01
I-AUC/G-AUC (pmol·mmol^{-1})	19 ± 14	37 ± 35	0.0004	0.004
Acute insulin response (pmol)[b]	260 ± 279	482 ± 566	0.017	0.045

QUICKI, Quantitative insulin sensitivity check index; G-AUC, glucose area under the curve; I-AUC, insulin area under the curve. To convert glucose to mg, divide mmol by 0.0555; to convert insulin to μIU/ml, divide pmol by 7.175.

[a] Adjusted for age and BMI (analysis of covariance).

[b] Acute insulin response = $(I_{4min} + I_{5min} + I_{6min} + I_{7min} + I_{8min})/4 - I_{0min}$.

BMI-matched normal women (8). Interestingly, in view of the present findings, a small study many years ago reported decreased insulin secretion in response to glucagons and tolbutamide in girls with TS (24). The present study compared normal-weight women with TS to age- and BMI-matched women with 46,XX POF and to normal women, aiming to isolate the genetic factors influencing glucose metabolism in TS from effects of adiposity and hypogonadism. In this study, we showed that insulin secretion was reduced and insulin sensitivity was actually better in women with TS compared with both groups of controls.

In conclusion, our findings show that impaired insulin secretion resulting in an increased prevalence of IGH is a primary feature of the Turner metabolic phenotype. Exclusion of secondary causes, such as altered body composition or sex steroid effect due to ovarian failure, implicates haploinsufficiency for unknown X-chromosome genes in this metabolic phenotype. Further studies are required to identify the X-chromosome locus and gene(s) responsible for this distinct metabolic phenotype.

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Address all correspondence and requests for reprints to: C. A. Bondy, Building 10/10N262, 10 Center Drive, National Institutes of Health, Bethesda, Maryland 20892. E-mail: bondyc@mail.nih.gov.

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