*Menopause: The Journal of The North American Menopause Society*
Vol. 13, No. 6, pp. 911-916
DOI: 10.1097/01.gme.0000248702.25259.00
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# Effects of ovarian failure and X-chromosome deletion on body composition and insulin sensitivity in young women

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**Abstract**

***Objective:*** Menopause is associated with increased visceral adiposity and reduced insulin sensitivity. It remains unclear whether these changes are due primarily to ovarian failure or aging. The aim of this study was to clarify the impact of ovarian failure on body composition and insulin sensitivity in young women.

***Design:*** In a cross-sectional study, we compared main outcome measures (body mass index, body composition by dual-energy x-ray absorptiometry, and insulin sensitivity by Quantitative Insulin Sensitivity Check Index) in three groups: women with 46,XX premature ovarian failure (POF), women with premature ovarian failure associated with 45,X or Turner syndrome (TS), and normal control women (NC). Participants were enrolled in National Institutes of Health Clinical Center protocols between years 2000 and 2005.

***Results:*** Mean body mass index (±SD) was lower in women with POF (n = 398): 24.3 ± 5 kg/m$^2$ versus 27.8 ± 7 for women with TS (n = 131) and 26.6 ± 4 for controls (n = 73) (both $P < 0.001$). Only 33% of women with POF were overweight or obese, compared with 56% of those with TS and 67% of NC women ($P < 0.0001$ for both). Despite less obesity, women with POF had lower insulin sensitivity (0.367 ± 0.03) compared with those with TS (0.378 ± 0.03, $P = 0.003$) and NC women (0.376 ± 0.03, $P = 0.04$). In groups selected for similar age and body mass index, women with POF (n = 89), women with TS (n = 48), and NC women (n = 40) had similar total body and trunk adiposity. After adjustment for age and truncal adiposity, women with POF had significantly lower insulin sensitivity than women with TS ($P = 0.03$) and NC women ($P = 0.049$).

***Conclusions:*** In contrast to observations in middle-aged postmenopausal women, ovarian failure in young women is not associated with increased total or central adiposity. In fact, women with TS were similar to NC women, whereas women with POF were leaner. The lower insulin sensitivity observed in women with POF deserves further investigation.

***Key Words:*** Adiposity – Turner syndrome – Premature ovarian failure – Menopause – Estrogen.

Received December 20, 2005; revised and accepted February 23, 2006.

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J. A. Yanovski, L. M. Nelson, and V. H. Vanderhoof are Commissioned Officers in the United States Public Health Service, Department of Health and Human Services.

This research was supported by the intramural research program of the National Institute of Child Health and Human Development, National Institutes of Health.

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Menopause is associated with an increase in body mass index (BMI) and a change toward more central obesity.[1-3] Because menopause is associated with adipose tissue redistribution toward a central concentration of fat, it may predispose women to insulin resistance and other components of the metabolic syndrome. The metabolic syndrome is characterized by central obesity, insulin resistance, and dyslipidemia and is considered a risk factor for cardiovascular disease. Adipose tissue metabolism in subcutaneous fat depots differs in perimenopausal and postmenopausal women in a manner that may predispose women to gain fat mass during menopause: basal lipolysis is lower and lipoprotein lipase activity is higher in postmenopausal women's abdominal and gluteal adipose tissues.[4] This difference seems to lead to an increase in trunk or intra-abdominal fat that is independent of age and total adiposity.[5]

Premature ovarian failure (POF) is an increasingly common condition today. This is due, in part, to the increasing number of girls and young women surviving cancer, many of whom experience ovarian failure as a result of cancer treatment.[6] Spontaneous, karyotypically normal POF affects at least 1% of women younger than 40 years.[7] Women with early natural menopause are reported to experience excess mortality from ischemic heart disease, although smoking may confound this association.[8] However, increased risk is also seen in young women with surgical menopause in some but not all studies.[9] As a potential explanation for increased cardiovascular risk, it is possible that alterations in body composition, ie, increased central adiposity and risk of the metabolic syndrome, may occur in young women with POF, as reported for women experiencing menopause at a later age.

There is little information about the effects of ovarian failure on body composition and insulin sensitivity in young women. One study reported that young women with primary amenorrhea without chromosomal aberrations had slightly increased body fat and a more centralized fat pattern compared with healthy controls and suggested that alterations in body composition and fat distribution could be considered as extragenital markers of ovarian failure.[10] European studies have reported that BMI, fat mass, and several components of the metabolic syndrome were greater in women with ovarian failure due to Turner syndrome (TS) than in age-matched controls.[11-13] To clarify the effects of POF and X-chromosome deletion on body composition in young women, in the present study we compared BMI, adiposity, and insulin sensitivity in groups of healthy volunteers with normal ovarian function, POF, and TS. Total and regional adiposity were assessed with dual-energy x-ray absorptiometry (DXA) to avoid confounding effects of altered body habitus in TS. Our surprising and unexpected finding was that POF occurring in young women does not lead to premature obesity or centralized adiposity and even seems to be associated with greater leanness in karyotypically normal women.

## METHODS

### Study participants

Our three study groups included women with TS; women with karyotypically normal, spontaneous POF; and healthy women with normal ovarian function. All study protocols were approved by the National Institute of Child Health and Human Development Institutional Review Board, and all participants gave written informed consent. Study participants with TS and POF were recruited primarily through notices on the Internet and the National Institutes of Health home page; healthy controls were recruited through these methods and via print and radio advertisements in the Washington, DC, region.[14] Normal women were required to be free of significant medical illnesses and to be taking no medications known to affect body weight on a regular basis. Women with TS had their diagnosis confirmed by a 50-cell peripheral karyotype in which more than 70% of cells demonstrated loss of all or part of the second sex chromosome. The karyotype distribution for this group was 67% 45,X; 19% 45,X/46,XX or 46XY; 10% 46,XiXq or 46,XiXq/45,X; and 4% 46,XdelXp or 45X/46,XdelXp. Women with POF had a history of at least 4 months of noniatrogenic amenorrhea at younger than 40 years of age at least two determinations of follicle-stimulating hormone levels greater than 40 mIU/mL (at least 1 month apart), and a normal, 46,XX 50-cell peripheral karyotype. Women participating in the TS and POF natural history or screening protocols discontinued hormone therapy 2 weeks before the study. Healthy control women had a history of normal menstrual cycles. These volunteers were compensated for their participation. All participants were in good general health and euthyroid as determined by physical examination and laboratory tests.

The first study phase included all women enrolling in the National Institute of Child Health and Human Development TS, POF, and normal volunteer protocols between the years 2000 and 2005. The data available for these women included weight, height, fasting blood sugar and insulin levels, medical history, and



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demographic information. The second phase of the study included TS, POF, and control groups that were matched for age and BMI by restricting inclusion to those 18 to 42 years of age with a BMI of 18 to 32 kg/m$^2$. All these women underwent DXA body composition studies in addition to measurements of the above-described data. For this phase of the study, women with POF were participating in the run-in phase of a hormone therapy protocol and were using a 100-μg transdermal estradiol patch. The great majority of women in both the TS and POF groups were white, so control women were also selected from among white volunteers. Women with a history of diabetes mellitus or use of medications known to affect carbohydrate metabolism were excluded from the study.

### Experimental procedures

Fasting glucose and insulin were measured for all women. Fasting glucose was measured by the Synchron LX system using an oxygen rate mechanism employing a Beckman oxygen electrode. Fasting insulin was measured using a chemiluminescence immunoassay on an Immulite analyzer. Body composition was determined using whole-body DXA (Delphi A, LX 20 Beckman, Bedford, MA, software version 11.2) performed in whole-body fan beam mode. Fasting insulin sensitivity was assessed using the Quantitative Insulin Sensitivity Check Index (QUICKI) = $1/[\log G_0 \text{ (mg/dL)} + \log I_0 \text{ (}\mu\text{U/mL)}]$.[15]

### Statistics

Group means of continuous outcome variables were compared by post hoc analysis of variance (age and BMI) or analysis of covariance (percentage of body fat and QUICKI) with age and BMI or age and percentage of truncal adiposity as covariates using Fisher's protected least significant difference *t* test and Bonferroni-Hochberg adjustment for multiple comparisons. Proportions were compared using a *z* test. Results are presented as mean ± SD or least squares means unless otherwise specified. Analyses were performed using Stat View version 5.01 (SAS Institute, Inc, Cary, NC) and SuperAnova version 1.11 (Abacus Concepts, Berkeley, CA).

## RESULTS

### BMI, obesity, and insulin sensitivity in women with TS, POF, and normal ovarian function

We first addressed the question of whether obesity is more prevalent among women with early ovarian failure. To this end, we compared BMI in all women aged 18 years and older who participated in the TS (n = 131) or POF (n = 398) natural history protocols from 2000 to 2005 and normal volunteer women, also aged 18 years and older (n = 73) (Table 1). Mean age was significantly greater in the TS group than in the other groups. Mean BMI was lower in the group with POF than in both other groups. Correspondingly, the prevalence of overweight and obesity was lower in the POF group (33.1%) than in the TS (55.5%) or normal control (NC) group (67.1%) (Table 1). Despite greater leanness as measured by BMI, insulin sensitivity was lower in the POF group than in both other, more obese groups.

### Adiposity in TS, POF, and NC groups

Given the apparent discrepancy between BMI and insulin sensitivity noted above, we hypothesized that BMI might not accurately reflect the degree, or perhaps the regional concentration, of adiposity in women with POF versus the other groups. To investigate this possibility, we used DXA to measure total and regional adiposity in groups with TS, POF, and normal ovarian function (Table 2). These groups were restricted to women aged 18 to 42 years and with

**TABLE 1.** *BMI and insulin sensitivity in unselected groups with Turner syndrome and premature ovarian failure*

| Group | NC (n = 73) | POF (n = 362) | TS (n = 119) | *P* value |
|---|---|---|---|---|
| Age (y) | 32.2 (7.0) | 32.2 (6.6) | 35.7 (11.3) | NC vs POF: 0.999; NC vs TS: 0.0038; POF vs TS: <0.0001 |
| BMI (kg/m$^2$) | 26.6 (3.6) | 24.3 (4.5) | 27.8 (7.2) | NC vs POF: 0.0008; NC vs TS: 0.093; POF vs TS: <0.0001 |
| Prevalence of overweight/obesity (BMI ≥25 kg/m$^2$) | 67.1% (95% CI: 56.3-77.9) | 33.1% (95% CI: 28.3-37.9) | 55.5% (95% CI: 46.6-67.0) | NC vs POF: <0.00001; NC vs TS: 0.116; POF vs TS: <0.00001 |
| QUICKI | 0.376 (0.03) | 0.367 (0.03) | 0.378 (0.034) | NC vs POF: 0.035; NC vs TS: 0.702; POF vs TS: 0.003 |

Data are in means (SD) for age and body mass index (BMI), and in least squares means (SD) for Quantitative Insulin Sensitivity Check Index (QUICKI), corrected for age and BMI. Means for age and BMI were compared by analysis of variance followed by Fisher's protected least significant difference. Analysis of covariance adjusted for age and BMI was used to compare QUICKI. Prevalence of overweight/obesity was compared by *z* test for proportions. NC, normal control group; POF, premature ovarian failure group; TS, Turner syndrome group.



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**TABLE 2.** *Adiposity and insulin sensitivity in age- and BMI-matched groups with normal ovarian function (controls) and with premature ovarian failure or Turner syndrome*

| Group | NC (n = 40) | POF (n = 89) | TS (n = 48) | *P* value |
|---|---|---|---|---|
| Age (y) | 30.3 (7.0) | 30.3 (5.3) | 29.8 (7.9) | NC vs POF: 0.9691; NC vs TS: 0.7265; TS vs POF: 0.6461 |
| BMI (kg/m$^2$) | 25.0 (3.2) | 24.0 (3.1) | 24.5 (4.1) | NC vs POF: 0.1322; NC vs TS: 0.5109; TS vs POF: 0.4131 |
| % Total body fat | 32.8 (5.5) | 31.6 (5.7) | 33.3 (6.4) | NC vs POF: 0.1159; NC vs TS: 0.5706; TS vs POF: 0.0194 |
| % Fat trunk | 29.9 (6.8) | 27.6 (6.8) | 30.0 (6.9) | NC vs POF: 0.078; NC vs TS: 0.941; TS vs POF: 0.050 |
| % Fat arm average | 34.2 (5.0) | 35.1 (5.0) | 39.2 (5.0) | NC vs POF: 0.325; NC vs TS: <0.0001; TS vs POF: <0.0001 |
| % Fat leg average | 37.9 (5.5) | 37.6 (5.5) | 38.7 (5.5) | NC vs POF: 0.750; NC vs TS: 0.473; TS vs POF: 0.232 |
| QUICKI | 0.380 (0.028) | 0.370 (0.028) | 0.380 (0.028) | NC vs POF: 0.050; NC vs TS: 0.977; TS vs POF: 0.041 |

Data are presented as means (SD) for age and body mass index (BMI) and as least squares means (SD) for the percentages of total body fat, truncal fat, arm fat average, and leg fat average and Quantitative Insulin Sensitivity Check Index (QUICKI). Means for age and BMI were compared by analysis of variance followed by Fisher's protected least significant difference. Analysis of covariance adjusted for age and BMI was used to compare percentage of body fat and QUICKI. NC, normal control group; POF, premature ovarian failure group; TS, Turner syndrome group.

BMI of 19 to 32 kg/m$^2$. The mean age for the three groups was ~30 years, and mean BMI was 24 to 25 kg/m$^2$. The total and regional depositions of fat were similar in the three groups, except for greater fat in the upper extremities in the TS group as compared with both the POF and NC groups (Table 2). The ratios of arm, trunk, and leg fat to total body fat mass were similar in the three groups (data not shown), suggesting that overall, regional patterns of fat distribution were similar. Despite our concern that BMI may not be an accurate predictor of adiposity in women with TS or POF, the relationship between BMI and adiposity as determined by DXA was not different among the three groups (Fig. 1A). Interestingly, as in the larger unselected groups, insulin sensitivity was lowest in the POF group. The negative relationship between central adiposity and insulin sensitivity was obvious and similar in slope and predictive value in TS and POF groups, but the set point for the curve was shifted upward in the TS group (Fig. 1B).

The similar body composition of the three BMI-identical groups suggests that there were no major differences in dietary or activity patterns that could explain the differences in insulin sensitivity. However, we do not have data on these behavior patterns to allow us to examine this possibility directly.

### Potential contributors to leanness in POF

Factors that might contribute to the greater leanness in the POF group were investigated. The number of years of formal education was similar in the three groups (mean, 16 ± 1 years) and was not correlated with total or regional adiposity (data not shown). BMI and adiposity were similar in married versus unmarried women with POF. Length of estrogen deficiency was not associated with adiposity in POF:

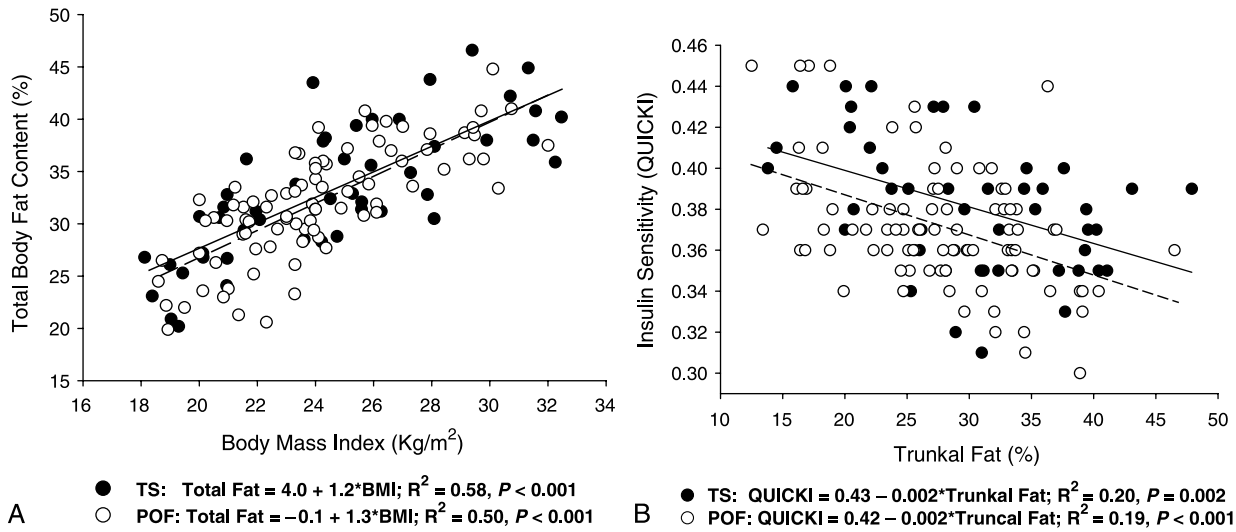


**FIG. 1.** (**A**) Similar correlations of body mass index (BMI) and total body fat in women with Turner syndrome (TS) and premature ovarian failure (POF). (**B**) Higher insulin sensitivity of women with TS for every level of adiposity compared to women with POF. TS (solid line); POF (dashed regression line).



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those with a history of 100 months or more of estrogen deficiency were similar in body fat to those with a history of 10 months or less of estrogen deficiency (data not shown).

## DISCUSSION

A primary goal of this study was to determine whether POF occurring in young women is associated with increases in central adiposity and risk of the metabolic syndrome, as seen in many older women experiencing menopause around the age of 50 years. Our study shows that BMI is not greater in women with POF compared with contemporaneous controls. On the contrary, women with karyotypically normal POF were remarkably lean. The average BMI for nearly 400 women participating in a protocol recruiting women with POF was 24.5 kg/m$^2$, and the prevalence of overweight/obesity (BMI $\geq$ 25 kg/m$^2$) in this group was ~37%, both of which are significantly lower than values for our NC group and for women of similar age residing in the United States, according to the most recent National Health and Nutrition Examination Survey data.[16] Women with TS were actually more similar to our NC women and to population norms in BMI and prevalence of obesity. Comparing groups identical in age and BMI, we found that total and central (truncal) adiposity were very similar in all three groups. Thus, POF occurring in young women does not lead to premature obesity or centralized adiposity and even seems to be associated with greater leanness in karyotypically normal women.

A secondary goal was to determine whether the increased obesity reported for medical clinic patients with TS would be found in free-living TS volunteers. We found that the average BMI and prevalence of overweight/obesity in women with TS in this study were similar to those of our NC group and to the US population.[16] According to 1999 to 2002 data, the age-adjusted prevalence of overweight/obesity was 65% in the whole US population, and the actual rate among women aged 20 to 39 years was 55%.[16] The prevalence of overweight/obesity in our TS population, aged 18 to 62 years, was 59%, and among women aged 20 to 39, 55%. Moreover, we found that total and truncal adiposity were similar in the NC and TS groups, although women with TS had selectively increased adiposity in the upper extremities. This latter finding is consistent with a previous DXA study in girls with TS.[17] Previous reports of increased obesity in TS have been based on medical clinic populations in the United Kingdom and Denmark[12,13,18,19] and thus may have been biased by increased numbers of obese women attending such clinics. One recent study from the United Kingdom reported that women with TS have an excess of total and visceral adipose tissue and hepatic fat compared with normal controls.[19] However, in this very small study, the women with TS were obese, whereas the controls were of normal weight, so it would be expected that obesity would be associated with increased visceral fat regardless of TS status. To determine whether women with TS have selectively increased visceral or centralized adiposity, we compared groups with similar BMI and found similar total and truncal adiposity in TS and control women.

A larger study from this same UK TS clinic[18] compared groups of unselected women with TS (n = 117) and POF (n = 30) to a group of age-matched normal volunteer women (n = 31), similar to the first phase of the present study. Ostberg et al.[18] reported an average BMI of 26.8 kg/m$^2$ for the TS group, slightly lower than we found. However, the average BMI of their normal control group was 23.7 kg/m$^2$, considerably lighter than normal women in the United States. Thus, although women with TS are more obese than normal controls in the United Kingdom, they are not more obese than normal women in the United States at present. The controls used in this study were from the Washington, DC, metropolitan area, but their adiposity was similar to that reported for women nationwide. We conclude that there is an unfortunate tendency toward increasing obesity among women with TS and women in general in the United States but that there is no distinctive effect of X-chromosome deletion on adiposity per se. Interestingly, the average BMI of the UK POF group (22.9 kg/m2) was somewhat lower than that of their normal control group,[18] although these two groups were not compared statistically. Women with TS in this UK study demonstrated significantly greater sensitivity to insulin compared with women with POF and normal controls despite their greater obesity.[18] This finding supports our previous work demonstrating greater insulin sensitivity in participants with TS as compared with women with POF and normal volunteers.[20] Our present data show better insulin sensitivity in TS compared with POF, but not NC women, leaving open the possibility that we are seeing relatively impaired insulin sensitivity in POF rather than enhanced insulin sensitivity in TS. It is important to note that the differences in insulin sensitivity were very small, with all values well within the normal range. Because this was a cross-sectional study, it is possible that altered insulin sensitivity preceded and potentially contributed to development of POF, although this seems a very unlikely scenario.



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The fact that women with 46,XX POF were significantly leaner than other groups was an unexpected finding. We did not obtain data on diet or activity patterns for the women in the present study. Future studies will need to investigate exercise and diet in these women to further elucidate the cause of the body weight and metabolic differences found in the three groups. Differences in insulin sensitivity between the POF and TS groups is not due to differences in estrogen treatment because significant differences are observed between the TS and POF groups that are both off estrogen treatment (Table 1), when the POF group is on estrogen and the TS group off estrogen (Table 2), and when both groups are on estrogen treatment, as demonstrated in the UK study.[18] The duration of ovarian failure was typically longer in TS, but there was no correlation between duration of ovarian failure and BMI or insulin sensitivity in POF. Moreover, this factor would not explain the differences between the POF and NC groups. A lack of effect of duration of ovarian failure on metabolic parameters was also found in the UK study comparing women with POF, TS, and controls.[13] Endogenous androgens may influence body composition, but both ovarian failure groups have reduced androgen levels.[21,22] Thus, the reasons that women with POF are relatively leaner and less insulin sensitive than controls and women with TS remain to be determined. Although all three BMI-matched groups had similar body composition by DXA, it is possible that women with POF had a selective accumulation of visceral fat, perhaps associated with increased levels of inflammation affecting insulin sensitivity.

## CONCLUSION

In summary, this study shows that young women with POF maintained on usual ovarian hormone treatment are not more obese and do not have greater total or central adiposity than women of the same age with normal ovaries. In addition, X-chromosome haploinsufficiency does not seem to cause greater total or central adiposity in women with TS compared to women with normal ovarian function who are similar in age and BMI. Thus, the development of centralized adiposity associated with the metabolic syndrome at the time of natural menopause is likely to be more related to aging and decreased physical activity level than to ovarian failure.

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