Effect of obesity on endogenous secretion of growth hormone in Turner’s syndrome

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Abstract
Nocturnal growth hormone secretion over a 12 hour period was assessed at 20 minute intervals in 25 prepubertal subjects with Turner’s syndrome and 11 normal prepubertal girls of short stature to try and elucidate the relationship between body weight and endogenous secretion of growth hormone in Turner’s syndrome. There were no differences in mean growth hormone concentration, age, height, or growth velocity between the two groups. There was an age related decline in mean growth hormone concentration in patient’s with Turner’s syndrome in contrast to the age related increase in controls. Mean percentage of ideal body weight was significantly higher in the Turner’s syndrome group than among controls and it increased with age. There was a strong inverse relationship between mean growth hormone concentration and percentage of ideal body weight in those with Turner’s syndrome. Covariate analysis of the multiple linear regression of mean growth hormone concentration on age and percentage of ideal body weight in Turner’s syndrome indicated that percentage of ideal body weight had a significant effect on endogenous secretion of growth hormone when age was held constant, but not the other way round.

We conclude that the age related decline in endogenous secretion of growth hormone in Turner’s syndrome is partly the result of increasing body weight with age. The significant influences of biological variables such as age and body weight in the interpretation of measurements of endogenous secretion of growth hormone in Turner’s syndrome should be emphasised.

Turner’s syndrome is the most common sex chromosomal disorder and it is characterised phenotypically by short stature, ovarian dysfunction, and other somatic features. The main sign, which affects almost all children with Turner’s syndrome, is short stature. Although its precise pathogenesis is not known, possible contributing factors include intrauterine growth retardation, growth failure during the first decade of life, primary hypogonadism, absent pubertal growth spurt, and skeletal abnormalities.3-7 More recently, age related growth hormone deficiency has been reported.5-7

Obesity is one of the somatic features of Turner’s syndrome, and the degree of obesity increases with age.4 8 9 Impaired endogenous secretion of growth hormone in both total output and pulse frequency, and decreased growth hormone response to pharmacological stimulation tests, have been observed in simple or idiopathic obese subjects though the mechanism remains unknown.10-13 Obesity has not been taken into account in interpreting the decline of endogenous secretion of growth hormone in Turner’s syndrome.5-7

The aim of the present study was to examine the relationship of age, obesity, and endogenous secretion of growth hormone in Turner’s syndrome.

Subjects and methods
All 25 prepubertal patients with Turner’s syndrome (age range 2.0–16.6 years) who were referred to this department between 1986 and 1987 were included in the study. The diagnosis of Turner’s syndrome was confirmed by culture of peripheral blood lymphocytes. The karyotype findings were: 45XO (n=13); 46X,i(Xq) (n=6); 45XO/46X,i(Xq) (n=2); 46X,i(Xp) (n=1); and 45XO/46XXr (n=3). Five of the 25 patients had previously had oxandrolone treatment for short stature for periods varying from six months to two years; all medications were stopped at least six months before the study. One patient had primary hypothyroidism and had been receiving thyroxine replacement for 18 months. All subjects were clinically and biochemically euthyroid at the time of sampling of growth hormone.

All 11 prepubertal girls (age range 4.1–13.1 years) with familial or constitutional short stature who were referred to this department for assessment of short stature during the same period (1986 and 1987) were included in the control group. All subjects were healthy, free from systemic disease, and had no evidence of endocrine abnormality. No subject had received growth promoting treatment before the study. Consent was obtained for the investigation.

PROTOCOL
All subjects were followed up at quarterly intervals for at least one year before the overnight growth hormone sampling. Auxological data were recorded at each visit. Height was measured with a Harpenden statimeter. Weight was measured on a scale with an accuracy of 0.1 kg. Each subject was admitted to the metabolic ward in the afternoon. No fasting or special diet was required. Patients received a normal dinner at 5.30 pm before which a 22G catheter was inserted into a forearm vein. Blood samples for measurement of growth hormone concentration...
were taken at 20 minutes intervals from 8.00 pm to 8.00 am the next morning. A total of 37 samples were collected. Plasma was immediately separated and stored at –20°C until assayed.

The growth hormone response to pharmacological stimulation was assessed after overnight sampling. Thirty two patients had an arginine stimulation test combined with an insulin hypoglycaemia stimulation test, and four patients had a clonidine stimulation test, after overnight fasting. Arginine 0·5 g/kg body weight (maximum 30 g) was given by intravenous infusion as a 10% solution in normal saline. Blood samples were collected at –15, 0, 30, 45, and 75 minutes. Short acting insulin (Actrapid, Novo) of 0·1 unit/kg body weight was then given intravenously; all patients achieved biochemical hypoglycaemia with serum glucose concentrations of <2·2 mmol/l. Blood samples were taken at 0, 15, 30, 45, 60, 75, 90, and 120 minutes. Clonidine 0·125 mg/m² was given orally; blood samples were taken every 30 minutes for 150 minutes.

Plasma was also taken for assessment of thyroid and renal function, and estimation of luteinising hormone, follicle stimulating hormone, oestradiol, and insulin-like growth factor I (IGF-1) concentrations. Bone age was assessed at the date of study and estimated by Greulich and Pyle’s method.14

ASSAYS
Growth hormone concentrations were measured by a radioimmunoassay (RIA) that was done by a double antibody technique with a sensitive and specific antiserum. The first antibody was a rabbit growth hormone antibody used at a final dilution of 1/1 000 000. Each sample was assayed in duplicate, and the mean value expressed in μg/l.15 All samples from one subject were measured in the same assay. The coefficients of variation between assays were 21·5% at the level of 2 μg/l; 8·5% at 8·5 μg/l, and 6·9% at 17·5 μg/l. The intra-assay coefficients were 10·6%, 5·3%, and 6·6%, respectively. The average minimum detectable concentration calculated from 40 assays was 0·14 μg/l (range 0·02–0·3).

Gonadotrophins and oestradiol were measured in duplicate with commercial immunoassay kits as follows: follicle stimulating hormone (Delfia hFSH kit; Pharmacia) with inter assay coefficient of variation of 8·3% at 23·1 IU/l and 10·4% at 4·2 IU/l; luteinising hormone (Delfia hLH kit; Pharmacia), inter assay coefficient of variation of 8·0% at 14·0 IU/l and 7·1% at 4·5 IU/l; oestradiol (125I-Estradiol Direct Radioimmunoassay Kit; Baxter Dade AG), with an interassay coefficient of variation of 8% at 252 pmol/l. The minimal detectable concentration of oestradiol was 18·5 pmol/l.

IGF-1 was measured by RIA,16 the inter assay coefficients of variation were 13·8% at 6·3 nmol/l, 8·7% at 36·3 nmol/l, and 14·3% at 171·6 nmol/l. The intra-assay coefficients of variation were 13·3% at 6·0 nmol/l, 11·8% at 31·8 nmol/l, and 14·6% at 207·6 nmol/l.

ANALYSIS OF OVERNIGHT GROWTH HORMONE PROFILES
Overnight growth hormone profiles were analysed using the PULSAR algorithm modified for growth hormone.17 The original PULSAR algorithm was designed particularly for the analysis of gonadotrophins,18 but (unlike gonadotrophins) the interpeak concentrations of growth hormone are usually undetectable with current assays.19 The modified PULSAR algorithm sets a smooth but variable baseline with a maximum of 1 μg/l. Peaks are defined as a subset of values of duration n above this baseline, all the points of which are at least G units of the SD of the RIA assay in magnitude. As n increases G decreases, so the program selects narrow high peaks and broad peaks that may be lower. The G(n) values used were the default figures given by Merriam and Wachter in the original PULSAR algorithm: G(1) 3·98, G(2) 2·40, G(3) 1·68, G(4) 1·24, and G(5) 0·93.

The following variables were computed: overall mean growth hormone concentration of 37 samples from the 12 hour measurement, peak amplitude, and the number of pulses.

AUXOLOGICAL DATA
Height SD scores, weight SD scores, and percentage of ideal body weight were derived according to National Center for Health Statistics growth standards.20 Birth weight SD scores were calculated according to gestation from the Australian data of Kitchen et al.21 Growth velocity was calculated over 12 months. Growth velocity SD scores for bone age were derived using the clinical longitudinal standards for height and height velocity for American children by Tanner and Davies.22

STATISTICAL ANALYSIS
SAS (System for Elementary Statistical Analysis) software was used to analyse the data.23 Results are shown as mean (95% confidence intervals (CI)) unless otherwise stated. Data for all variables except weight SD scores, percentage of ideal body weight, and luteinising hormone and follicle stimulated hormone concentrations were normally distributed, so group means were compared by Student’s t test and differences between means given with 95% CI in parentheses; associations were assessed with linear regression and correlation; multiple linear regression was used to examine inter-relationships between variables after controlling for covariates, and to test whether the slopes of the linear regressions were the same in both groups by testing for statistical interaction. For skewed distributions we used Wilcoxon’s rank sum test to compare the two groups, and medians are given; associations were examined by Spearman rank correlations. Fisher’s exact test was used to compare proportions in the two groups. All significance tests are two sided and probabilities of less than 0·05 were accepted as significant.

Results
The girls with Turner’s syndrome were older
than the controls though there were no significant differences in chronological age, bone age, age for height, height SD score, growth velocity SD score, or birth weight SD score between those with Turner's syndrome and controls (table 1). Bone age was delayed in both groups, but there was no significant difference in the degree of delay (table 1). There were no significant differences in any of the variables between the 13 girls with karyotype 45XO and the other 12 subjects who had either mosaicism or abnormal X chromosome.

The weight SD score was significantly higher in those with Turner's syndrome than controls (p=0.003) (table 1). The difference in percentage of ideal body weight between those with Turner's syndrome and controls was also highly significant (p=0.0001) (table 1). Fourteen girls with Turner's syndrome had percentage of ideal body weight greater than 120% and were defined as obese; 21 but none of the subjects in the control group had a percentage of ideal body weight of more than 120%. Obese subjects were older than non-obese subjects (p=0.002, table 2). There were, however, no significant differences in height SD score, bone age, and mean delay between chronological age and bone age between obese and non-obese patients (table 2).

There was no significant difference in plasma oestradiol concentrations between those with Turner's syndrome (mean: 52.8 pmol/l, 95% CI: 43.1 to 64.5 pmol/l) and controls (mean: 46.4 pmol/l, 95% CI: 32.4 to 60.5 pmol/l). Plasma oestradiol concentrations did not correlate with measurements of endogenous growth hormone output in either group. Plasma gonadotrophins concentrations were significantly higher in those with Turner's syndrome than in controls (follicle stimulating hormone: mean 32.1, 95% CI 22.0 to 42.3 IU/l compared with mean 1.3, 95% CI 0.6 to 2.1 IU/l, p=0.001; luteinising hormone: mean 7.1, 95% CI 4.5 to 9.6 IU/l compared with mean 0.3, 95% CI 0.1 to 0.5 IU/l, p=0.0001).

### Table 1: Clinical data of 25 patients with Turner's syndrome and 11 control subjects with familial or constitutional short stature

<table>
<thead>
<tr>
<th>Patients with Turner's syndrome (n=25)</th>
<th>Control subjects (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>95% CI</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>Chronological age (years)</td>
<td>10.2</td>
</tr>
<tr>
<td>Bone age (years)</td>
<td>9.1</td>
</tr>
<tr>
<td>Mean delay between chronological age and bone age (years)</td>
<td>1.7</td>
</tr>
<tr>
<td>Height SD score</td>
<td>-3.3</td>
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<tr>
<td>Birth weight SD score according to gestational age</td>
<td>-1.4</td>
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<tr>
<td>Growth velocity SD score according to bone age</td>
<td>-3.4</td>
</tr>
<tr>
<td>Weight SD score</td>
<td>-1.2</td>
</tr>
<tr>
<td>Percentage of ideal body weight</td>
<td>127.8</td>
</tr>
</tbody>
</table>

*p=0.003; **p=0.0001.

### Table 2: Comparison of obese and non-obese patients with Turner's syndrome

<table>
<thead>
<tr>
<th>Obese (n=14)</th>
<th>Non-obese (n=11)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.8</td>
<td>10.7 to 12.9</td>
</tr>
<tr>
<td>Bone age (years)</td>
<td>9.8</td>
<td>9.0 to 10.7</td>
</tr>
<tr>
<td>Mean delay between chronological age and bone age (years)</td>
<td>2.2</td>
<td>1.5 to 2.9</td>
</tr>
<tr>
<td>Height SD score</td>
<td>-3.3</td>
<td>-2.8 to -3.7</td>
</tr>
<tr>
<td>Mean growth hormone concentration (µg/l)</td>
<td>1.7</td>
<td>1.2 to 2.2</td>
</tr>
<tr>
<td>No of pulses</td>
<td>3.5</td>
<td>2.8 to 4.2</td>
</tr>
<tr>
<td>Peak amplitude (µg/l)</td>
<td>11.5</td>
<td>7.7 to 15.4</td>
</tr>
</tbody>
</table>

### Table 3: Mean overnight growth hormone profiles in 25 patients with Turner's syndrome and 11 control subjects with familial or constitutional short stature

<table>
<thead>
<tr>
<th>Patients with Turner's syndrome (n=25)</th>
<th>Control subjects (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>95% CI</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>Mean growth hormone concentration (µg/l)</td>
<td>2.1</td>
</tr>
<tr>
<td>Peak amplitude (µg/l)</td>
<td>13.9</td>
</tr>
<tr>
<td>No of pulses</td>
<td>4.2</td>
</tr>
</tbody>
</table>

GROWTH HORMONE SECRETION

There were no significant differences between patients with Turner's syndrome and controls for any of the variables computed from overnight growth hormone profiles (table 3), and none of the variables correlated significantly with height SD score or growth velocity SD score in either group.

In two of the 11 controls (18%) and nine of the 25 with Turner's syndrome (36%) the peak amplitude of their nocturnal growth hormone profiles was suboptimal (<10 µg/l), but not significantly so (p=0.44). Nine of the 25 subjects with Turner's syndrome (36%) had suboptimal peak growth hormone responses to pharmacological stimulation (<10 µg/l) but none of the control subjects showed an abnormal response (p=0.03). Four children with Turner's syndrome had suboptimal growth hormone responses in both endogenous growth hormone profile and pharmacological stimulation tests.

There was no significant correlation between...
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The peak growth hormone response from pharmacological stimulation tests and any of the measurements made from overnight growth hormone profiles in either group. The peak growth hormone concentration after the pharmacological stimulation test did not correlate with any of the auxological variables (including body weight) or with age.

IGF-1 concentrations increased with age in patients with Turner’s syndrome (r=0.46, p=0.01) (fig 1A) but not in controls, though a comparison of the linear regression between the two groups was not significant (p for difference between slopes =0.08). IGF-1 was significantly higher in those with Turner’s syndrome than in controls (mean 19.8, 95% CI 16.9 to 23.2 nmol/l) compared with mean 13.7, 95% CI 10.7 to 16.6 nmol/l; p=0.03) (fig 1B). Because girls with Turner’s syndrome were slightly older, we examined the relationship between IGF-1 concentration and age by taking age difference into account; after controlling for the difference in age between the two groups, the IGF-1 concentration was 4.7 nmol/l (95% CI: 0–6 to 10.0 nmol/l) higher in those with Turner’s syndrome than in controls (p=0.09). Eleven of the 25 patients with Turner’s syndrome (44%) and four of the controls (36%) had IGF-1 concentrations lower than the laboratory’s reference range (<2SD scores for age). IGF-1 concentrations had no association with either auxological data or measurements of endogenous growth hormone profiles.

**Effect of Age**

There was a highly significant difference in the relationship between mean growth hormone concentration and age for those with Turner’s syndrome and controls (p for difference between slopes =0.005). In those with Turner’s syndrome there was a significant age-related decline in mean growth hormone concentration (r=–0.41, p=0.04) (fig 2) and peak amplitude (r=–0.50, p=0.01); in contrast, there was an age-related increase in the control group (fig 2).

**Effect of Obesity**

There was a highly significant age related increase in percentage of ideal body weight in patients with Turner’s syndrome (r=0.57, p=0.003) (fig 3A). Two of the girls with Turner’s syndrome had extremely high values, which tend to skew the distribution and exaggerate the relationship with age. If these two points are omitted, percentage of ideal body weight increases by 2.2% (95% CI 0.7 to 3.7%) with each year of age (p=0.01); after adjusting for age, percentage of ideal body weight was 18.0% higher in Turner’s syndrome (95% CI 9.2 to 26.9) than in controls (p=0.0002). There was no significant correlation between age and percentage of ideal body weight in controls (fig 3B).

There was also a significant weight-related decline in endogenous secretion of growth hormone in those with Turner’s syndrome (fig 4), and this relationship was not altered when the two extremely obese girls were omitted from the analysis (r=–0.52, p=0.02). In Turner’s syndrome this decline was observed in all measurements of overnight growth hormone profiles: mean growth hormone concentration (r=–0.62, p=0.0009) (fig 4A), peak amplitude (r=–0.54, p=0.0006), and the number of pulses (r=–0.52, p=0.008). The relationship between percentage of ideal body weight and endogenous secretion of growth hormone in Turner’s syndrome is further illustrated in figure 5. There was no significant association between mean growth hormone concentration and percentage of ideal body weight in controls (fig 4B).

The difference in overnight growth hormone profiles between obese (n=14) and non-obese (n=11) patients with Turner’s syndrome was significant. Obese subjects had fewer pulses and
lower mean growth hormone concentrations than non-obese patients (table 2).

**COVARIATE ANALYSIS**

Because both age and body weight had significant effects on endogenous secretion of growth hormone, the inter-relationships among these three variables in Turner’s syndrome were further explored by multiple linear regression of mean growth hormone concentration on age and percentage of ideal body weight. The effect of percentage of ideal body weight on mean growth hormone concentration remained significant after controlling for age (p=0.005), but age had no significant effect on mean growth hormone concentration after adjusting for percentage of ideal body weight.

**Discussion**

This study confirms that there is an age related decline in endogenous secretion of growth hormone in prepubertal subjects with Turner’s syndrome. This decline contrasts with the increase in endogenous secretion of growth hormone in the prepubertal subjects who were controlled for the same sex, were of similar age, and had similar height and growth velocity SD scores. Massarano et al reported this finding, though their study lacked controls. The aetiology of this decline in endogenous secretion of growth hormone is unknown.

Primary hypogonadism in Turner’s syndrome may have a crucial role. Endogenous oestradiol is thought to be important in the pulsatile amplification of endogenous secretion of growth hormone in normal adults. Physiological doses of oestradiol enhance the endogenous secretion of growth hormone in castrated and intact female baboons. Suppression of ovarian function in girls with central precocious puberty results in decreased endogenous secretion of growth hormone. Conflicting results have been reported in girls with Turner’s syndrome who were treated with physiological doses of oestrogen, whereas enhancement of endogenous secretion of growth hormone was noted in one study, no change was found in another. In the present study we found no difference in the plasma oestradiol concentration between prepubertal subjects with Turner’s syndrome and prepubertal normal controls of short stature. No correlation between plasma oestradiol concentrations and measures of endogenous growth hormone in patients with Turner’s syndrome. The possibility that oestradiol may have a role in the decline of endogenous growth hormone had not, however, been totally excluded as primary hypogonadism was evident in patients with Turner’s syndrome from the raised gonadotrophin concentrations.

Obesity is difficult to define but easy to recognise; it is defined here as more than 120% of ideal weight for height. Normal weight standards in children, however, remain difficult to determine. There are several methods of estimating fatness in childhood. Estimation of body composition from anthropometric measurements are both practicable and useful. We prefer percentage ideal body weight rather than body mass index (weight/height²), as percentage ideal body weight not only takes height into account, but also provides easily recognised results. More than half the patients with Turner’s syndrome in this study were compared with none of the subjects in the control group. As the subjects were selected by their presentation to an endocrine clinic because of short stature not because of their body weight, this finding could be interpreted as indicating that there was a high incidence of obesity in prepubertal subjects with Turner’s syndrome. Obesity in Turner’s syndrome is age related, as indicated in this and several previous studies. With simple obesity, there is a strong inverse relationship between body weight and a number of measures of growth hormone in nocturnal growth hormone profiles (mean growth hormone concentration, peak amplitude, and pulse frequency). Covariate analysis indicated that the decline in endogenous secretion of growth hormone in Turner’s syndrome was strongly related to obesity but not to age. We believe therefore that obesity could partly explain the decline of growth hormone secretion in patients with Turner’s syndrome.

The possibility that obesity is causally related
to the decrease in endogenous growth hormone must be considered. Growth hormone stimulates lipolysis, which explains the decrease in subcutaneous fat in growth hormone deficient children being treated with growth hormone supplement.39 Adult subjects with growth hormone deficiency tend to be obese with decreased muscle mass, but no clear association has been made between growth hormone deficiency and obesity in childhood. Obesity was not mentioned in original descriptions of growth hormone deficiency, although children with hypopituitarism tend to have more fat in some regions of the body. Furthermore, the response of growth hormone to pharmacological stimuli is enhanced in obese subjects with no clinical evidence of growth hormone deficiency if they lose weight.33 We believe, therefore, that obesity is a cause rather than a consequence of growth hormone deficiency in the girls with Turner’s syndrome.

The total amount of growth hormone secreted is related to the pulse amplitude and frequency. The change in growth hormone secretion with age, stature, and pubertal stage is said to be a function of the pulse amplitude but not of its frequency.34 In contrast, the decline in secretion of growth hormone in simple obesity and in the present study in Turner’s syndrome was associated with decreased pulse frequency as well as amplitude. This association between body weight and diminishing pulse frequency in obese subjects suggests an abnormality in the hypothalamic control of growth hormone secretion through growth hormone releasing hormone and somatostatin.35 Speculation on the mechanism of this decrease in growth hormone pulse frequency has focused on the negative feedback of high plasma IGF-I or high free fatty acid concentrations, or both.36 37 Our data do not confirm the hypothesis about IGF-1 concentrations because although they were higher in patients with Turner’s syndrome than in controls, they were at the lower end of the reference range for the prepubertal age group. An alternative explanation for the decreased pulse frequency is that the sensitivity of the growth hormone assay does not allow us to detect low amplitude pulses occurring at normal frequency.19 Prepubertal children with simple obesity are usually tall for their age, and have advanced bone age.39 Our findings in obese prepubertal subjects with Turner’s syndrome, however, contrast with findings in subjects with simple obesity as there was no difference in height SD scores, bone age, or growth velocity between obese and non-obese groups.

It may be postulated that there is a connection between growth hormone secretion status and short stature in Turner’s syndrome because of the concomitance of decline in endogenous growth hormone secretion and severe growth retardation in prepubertal girls with Turner’s syndrome. We could not find any association between measures of growth hormone secretion and growth, and this supports the observations made by Massarano et al.2 Furthermore, the fact that subjects with Turner’s syndrome require a higher dose of exogenous growth hormone than subjects with growth hormone deficiency to achieve the same growth velocity suggests the possibility of partial end organ resistance to growth hormone in Turner’s syndrome, rather than clinical growth hormone deficiency.40

The plasma concentration of IGF-1 depends on age, growth hormone, and nutrition.41-45 A normal growth hormone-IGF-1 axis has been suggested in patients with Turner’s syndrome.46 In the present study, the plasma concentrations of IGF-1 in those with Turner’s syndrome were not totally dependent on growth hormone concentrations. Subjects with Turner’s syndrome had age related increases in IGF-1 despite the age related decline in growth hormone concentrations. This discrepancy has been commented on in Turner’s syndrome47 and in simple obesity.48 49 Although we found no direct relationship between IGF-1 and percentage of ideal body weight, it is apparent that obesity must be considered a regulating factor of circulating IGF-1 concentrations. The possibility that the interrelationship between growth hormone secretion, IGF-1, and nutrition is mediated by the nutritional regulation of the growth hormone receptor is currently being investigated.48

In conclusion, our study has confirmed the existence of an age related decline in secretion of growth hormone and increasing obesity in prepubertal children with Turner’s syndrome. This decline in endogenous secretion of growth hormone of can be attributed to the increased body weight in girls with Turner’s syndrome. We emphasise that the interpretation of endogenous growth hormone secretion requires critical assessment of biological variables including age, puberty, and weight.

This work partly fulfills the requirements for the degree of Master of Medicine (PW Lu) and was supported by the Postgraduate Research Awards from the University of Sydney.

We are indebted to the staff of the metabolic ward, Royal Alexandra Hospital for Children, Camperdown, to Mr B Kreuzman for oestrogen assays and to Mr Peter Greenacre for computing assistance. We also thank Dr R Baxter and Mr K Tan for measuring IGF-1 concentrations.

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