Women with Turner syndrome are at high risk of lifestyle-related disease —From questionnaire surveys by the Foundation for Growth Science in Japan

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Abstract. In this study, the prevalence of obesity and complications of lifestyle-related diseases, such as diabetes mellitus, hypertension, dyslipidemia and liver dysfunction, as well as the relationship with karyotypes, were investigated in 492 patients with Turner syndrome (TS) aged 17 years or older. Data were obtained through questionnaire surveys administered by attending physicians throughout Japan. Collected data were compared with data from the National Health and Nutrition Survey. Patient ages ranged from 17.1 to 42.5 years (mean ± standard error, 26.6±0.2). The prevalence of lifestyle-related diseases at age 20 or over was 6.3% for diabetes, 8.7% for hypertension, 20.2% for dyslipidemia and 12.4% for liver dysfunction. These four diseases were clearly associated with severity of obesity. Obesity (BMI ≥25 kg/m²) was observed in 106 out of 426 patients with TS aged 15 to 39 years (24.7%) and the prevalence was significantly higher than that of the general female population (9.4%). The mean BMI in age subgroups without any complications ranged from 21.2 to 22.7, which although was within normal ranges was significantly higher than that in the general female population (20.3–21.3). In this study population, patients with TS had more complications related to lifestyle-related diseases that were highly related to obesity. Few associations between complications and karyotypes were found. In the follow-up of patients with TS, the presence of lifestyle-related disease should be considered in the evaluation and treatment of the disease.

Key words: Turner syndrome, Lifestyle-related disease, BMI, Karyotype, Birth weight

TURNER SYNDROME (TS) is likely to have various complications involving the metabolic, autoimmune, cardiovascular, urinary system, bone and joint, otolaryngological, central nervous systems, and psychosocial diseases in addition to short stature and amenorrhea [1-4].

In this study we have focused on BMI, lifestyle-related diseases such as diabetes mellitus, hypertension, dyslipidemia and liver dysfunction in women with TS. Since TS is a relatively rare disease, it was difficult to investigate the relations between frequency of lifestyle-related disease and BMI, birth weight or karyotypes at a single medical facility. Especially, there are no report regarding the comparison of lifestyle-related disease between TS women and general female population.

The Foundation for Growth Science (FGS) in Japan has evaluated indications for growth hormone (hGH) treatment since 1986. Since physicians have registered their TS women with short stature nationwide, the majority of cases were available for follow up at FGS. Many physicians cooperated with our survey and responded to the questionnaire. We obtained a good deal of information of lifestyle-related disease which is very important and meaningful for physicians and researchers engaged in treatment and studies of women with TS.

Materials and Methods

The subjects were women with TS who were born on or before August 1, 1993 (17 years and older as of August 1, 2009), and had received hGH treatment for short stature.

We asked their attending physicians to respond to
the questionnaire shown in the Table 1.

In this study, we investigated the relationship between BMI and the single or combined complications of lifestyle-related disease such as diabetes mellitus, hypertension, dyslipidemia and liver dysfunction as well as the relationship between gestational ages, birth weight and these diseases. BMI and the prevalence of lifestyle-related disease in TS was compared with those of general female population. We also examine the association between karyotype and lifestyle related disease.

The survey was conducted in 544 facilities with 1656 cases. When the obtained data were insufficient, they were supplemented with a database from FGS. To use each data for academic purposes, agreement was obtained at the registration to FGS.

In the statistical analysis, for comparison of frequencies or of the mean values of groups the Fisher Randomization Test or the Mann-Whitney U test were used. Statistical significance was accepted at $P<0.05$ and JMP version 9.0.2 (SAS Institute Inc.) was used.

Table 1 A sheet for questionnaire survey in Turner syndrome

| Serial No. | Name of institute | Dr. in attendance |
|------------|------------------|------------------|
| Patient name | Date of birth | yr/mo/day |
| Registration No. | | |

(1) Please fill out following section.

Time when bone age reached around 14yr | 1yr later | 2yrs later | 3yrs later | 4yrs later | 5yrs later | 6 yrs later* | latest data |
|---|---|---|---|---|---|---|---|
| yr/mo/day | | | | | | | |
| body height | | | | | | | |
| body wt | | | | | | | |
| chronol. age | | | | | | | |
| bone age | | | | | | | |

* 1 to 6 years after the bone age reached around 14 yr.

(2) Presence or absence of complications

Please circle to appropriate one and fill out the blank.

1) Diabetes mellitus (Yes · No · Unknown) → Treatment (insulin or oral antidiabetic agent)
   Its type (1, 2, others), anti-pancreatic antibody (Yes · No)
2) Hypertension (Yes · No · Unknown) → Treatment (Yes · No)
3) Dyslipidemia (Yes · No · Unknown) → Treatment (Yes · No)
4) Liver dysfunction (Yes · No · Unknown) → Name of disease ( )
5) Other complications (Yes · No · Unknown) →
SEM, N=52) and 20.3±0.2 (Mean ± SEM, N=131) for 15–19 years and 23.0±0.2 (N=265) and 20.7±0.2 (N=284) for 20–29 years, and 22.9±0.3 (N=108) and 21.3±0.2 (N=499) for 30–39 years. BMI level in TS was significantly higher than the general female population for each age group (all P<0.001) [5]. The overall mean BMI in Turner women aged 20 years or older in this study was 23.0±0.2 (N=374). In Turner women, no significant difference was found among the age groups. BMI in one Turner woman aged ≥ 40 years was 26.0.

In Japan, obesity is defined as BMI ≥25 kg/m², subgrouped into class I (≥25 and <30); class II (≥30 and <35), class III (≥35 and <40), and class IV (≥40) [6], while underweight and normal range were as BMI <18.5, and ≥18.5 and <25, respectively. This classification differs from that by World Health Organization; preobese as BMI ≥25 and <30, and obesity as BMI ≥30 [7].

For all women with TS, there were 35 underweight (8.2%), 285 normal range (66.9%), 84 obesity class I (19.7%), 20 obesity class II (4.7%), 1 obesity class III (0.2%), and 1 obesity class IV (0.2%).

When the prevalence of obesity (BMI ≥25) by age group was compared between TS and general female population, it was found in 17.3% (9/52 cases) and 3.8% (5/131) of those 15–19 years of age, 26.0% (69/265) and 7.7% (22/284) of those 20–29 years of age, 25.0% (27/108) and 11.8% (59/499) of those 30–39 years of age (Table 2) [5], 24.7% (105/425) and 9.4% (86/914) of those 15–39 years of age, respectively. All of these prevalence were significantly higher in TS than in the same age groups of the general female population (P<0.01–0.001) [5].

b) Diabetes mellitus

Diabetes mellitus is defined as the HbA1C of 6.9% and over and/or the subject presently under the treatment of DM [5]. Diabetes was found in 24 of 440 TS cases (5.5%). In these cases, 19 cases were considered to be type 2 and there was no case of type 1.

By age group, diabetes was found in 0% (0/62 cases) of those 15–19 years of age, 5.1% (14/272) of those 20–29 years of age, 9.5% (10/105) of those 30–39 years of age, and 0% (0/1) of those 40 years of age or older. Although exact statistical analysis is difficult, as a reference data the prevalence in general female population aged 20–29 and 30–39 years in Japan was 0.7% (1/141 cases) and 0.9% (3/338) [5] (Table 2). The prevalence of adult subjects (20-39 yrs) in TS was 6.3% and was 0.8% in general female population.

| Diseases            | Age groups | Turner syndrome | General female population [5] |
|---------------------|------------|-----------------|-------------------------------|
| Obesity             | 15-19 years | 17.3%           | 3.8%                          |
|                     | 20-29 years | 26.0%           | 7.7%                          |
|                     | 30-39 years | 25.0%           | 11.8%                         |
| Diabetes mellitus   | 15-19 years | 0.0%            | -                             |
|                     | 20-29 years | 5.1%            | 0.7%                          |
|                     | 30-39 years | 9.5%            | 0.9%                          |
| Hypertension        | 15-19 years | 1.7%            | -                             |
|                     | 20-29 years | 6.6%            | 2.0%                          |
|                     | 30-39 years | 12.9%           | 6.4%                          |
| Dyslipidemia        | 15-19 years | 11.5%           | -                             |
|                     | 20-29 years | 18.2%           | 1.4%                          |
|                     | 30-39 years | 24.5%           | 2.4%                          |
| Liver dysfunction   | 15-19 years | 6.5%            | -                             |
|                     | 20-29 years | 11.4%           | 2.9%                          |
|                     | 30-39 years | 14.7%           | 1.6%                          |
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BMI was 24.7±1.2 (Mean ± SEM, N=22, 18.0–41.4) in cases with diabetes and 22.9±0.2 (N=369, 14.8–39.3) without diabetes (Table 3). No significant difference was found between the two groups. As for the relationship between diabetes and BMI (Fig. 1a), the prevalence of diabetes did not change in the BMI range of 15–24.9 but increased rapidly at ≥25.

c) Hypertension

In Japan, hypertension is defined as systolic blood pressure of ≥140 or diastolic blood pressure of ≥90 [5]. Hypertension was found in 31 of 404 cases (7.7%). By age group, hypertension was found in 1.7% (1/59 cases) of those 15–19 years of age, 6.6% (16/243) of those 20–29 years of age, 12.9% (13/101) of those 30–39 years of age (Table 2), and 100% (1/1) of those 40 years of age or older. The prevalence of hypertension in the general female population for 20-29 and 30-39 years of age were 2.0% (3/149 cases) and 6.4% (22/346), respectively [5] (Table 2). In these subjects aged 20 or over, the prevalence was also higher in TS (8.7%) than in normal female population (5.1%). BMI was 25.5±0.9 (Mean ± SEM, N=29, range 17.1–33.1) in cases with hypertension and 22.9±0.2 (N=333, range 14.8–41.4) in the cases without hypertension (Table 3), and the former value was significantly higher than the latter (P<0.05). As for the relationship between hypertension and BMI (Fig. 1b), the prevalence of hypertension did not change with BMI up to 24.9, as with diabetes, and increased rapidly with a BMI of ≥25.

d) Dyslipidemia

Dyslipidemia is defined as LDL cholesterol of ≥140, triglyceride of ≥150, or HDL cholesterol of <40 mg/dL [5]. Dyslipidemia was found in 82 of 433 cases (18.9%). By age group, it was found in 11.5% (7/61 cases) of those 15–19 years of age, 18.2% (49/269) of those 20–29 years of age, 24.5 % (25/102) of those 30–39 years of age (Table 2), and 100% (1/1) of those 40 years of age or older. The prevalence in general female population was 1.4% (2/144) for 20-29 years and 2.4% (8/337) for 30-39 years of age (Fig. 1c). In these subjects aged 20 or over, the prevalence was also higher in TS (20.2%) than in normal female population (5.1%). BMI was 24.5±0.4 (Mean ± SEM, N=74, range 17.1–34.8) in cases with dyslipidemia and 22.6±0.2 (N=310, range 14.8–41.4) in cases without dyslipidemia (Table 3) and the former value was significantly higher than the latter. The relationship between dyslipidemia and BMI differed from that with diabetes and hypertension (Fig. 1c). The prevalence started to increase in the BMI range of 20.0–24.9 and increased rapidly with further increases in BMI.

e) Liver dysfunction

Liver dysfunction is defined as AST of ≥41 U/L, ALT of ≥36 U/L, or γ-GTP of ≥60 U/L [5]. Liver dysfunction was found in 51 of 442 cases (11.5%). By age group, it was found in 6.5% (4/62

| Table 3 Comparison of BMI (kg/m²) between groups with or without complications |
|----------------------------------|-----------------|-----------------|-----------------|
|                                   | Complication (+) | Complication (−) | Significance |
|----------------------------------|-----------------|-----------------|-----------------|
| N | Mean ± SEM | N | Mean ± SEM | N | Mean ± SEM | N | Mean ± SEM |
|----------------------------------|-----------------|-----------------|-----------------|
| Single complication              |                 |                 |                 |
| Diabetes Mellitus (DM)           | 22              | 24.7±1.2        | 369             | 22.9±0.2        | P=0.15                      |
| Hypertension (HT)                | 29              | 25.5±0.9        | 333             | 22.9±0.2        | P<0.05                      |
| Dyslipidemia (DL)                | 74              | 24.5±0.4        | 310             | 22.6±0.2        | P<0.001                     |
| Liver dysfunction (LD)           | 47              | 25.7±0.7        | 346             | 22.6±0.2        | P<0.001                     |
| Two complications                |                 |                 |                 |
| LD & DL                          | 26              | 25.2±0.7        | 284             | 22.3±0.2        | P<0.01                      |
| HT & DL                          | 15              | 25.5±1.2        | 275             | 22.6±0.2        | P<0.01                      |
| HT & DM                          | 6               | 26.1±2.0        | 313             | 22.8±0.2        | P=0.1                       |
| LD & HT                          | 7               | 27.6±1.6        | 291             | 22.5±0.2        | P<0.01                      |
| LD & DM                          | 5               | 27.8±3.8        | 324             | 22.5±0.2        | P<0.07                      |
| DM & DL                          | 8               | 28.3±0.7        | 295             | 22.6±0.2        | P<0.01                      |
| Three complications              |                 |                 |                 |
| LD & HT & DL                     | 5               | 26.4±2.0        | 251             | 22.4±0.2        | P<0.001                     |
| LD & DM & DL                     | 3               | 26.6±0.5        | 271             | 22.4±0.2        | P<0.001                     |
| HT & DM & DL                     | 3               | 30.4±0.8        | 263             | 22.6±0.2        | P<0.001                     |

No patient had all complications.
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cases) of those 15–19 years of age, 11.4% (31/270) of those 20–29 years of age, 14.7% (16/109) of those 30–39 years of age (Table 2), and 0% (0/1) of those 40 years of age or older. The prevalence of liver dysfunction (abnormality of γ-GTP) in the general female population aged 20–29, 30–39 years were 2.9% (3/105) and 1.6% (5/321), respectively [5] (Table 2). In these adult ages, the prevalence was also higher in TS (12.4%) than in normal female population (1.9%). In the latter, the prevalence of abnormal AST (2.3%) and ALT (1.2%) values were similarly low.

BMI in the cases with liver dysfunction (25.7±0.7, N=47) was significantly higher than that in the cases without liver dysfunction (22.6±0.2, N=346) (P<0.001) (Table 3). As for the relationship between liver dysfunction and BMI, the prevalence started to increase in the range of 20.0–24.9 as was seen in dyslipidemia, and then rapidly increased with further increment of BMI (Fig. 1d).

f) Multiple complications of the above four diseases

We have investigated the relationship between multiple complications of lifestyle-related diseases and BMI. As shown in (Table 3), except for the combinations of diabetes and hypertension or diabetes and liver dysfunction, which were fewer in numbers, BMI levels in any combinations were higher than those of groups without complications (P<0.01). Except for the combination of liver dysfunction and dyslipidemia, BMI levels in any combinations were significantly higher than those of group with single complication. Combination of three diseases was found in three different ways and BMI levels in any combination were significantly higher than those of group without complications. Overall, 116 cases had complications. Among those cases, BMI levels were 24.0±0.5 (N=71) in cases with an either single complication, 24.9±0.8 (N=34) in cases with either two, and 27.5±1.0 (N=11) in cases with either three. BMI levels in any of these cases were significantly higher than those in 310 cases without any complications (22.2±0.2) (all, P<0.001). Although no significant difference was found between groups with a single complication and two complications, BMI in the group with three complications was significantly higher than those in the former two groups (P<0.01 and P<0.05). There were no cases with four complications. It is interesting that mean BMI value in TS women without any complication was significantly higher than those in general female population mentioned above through each age group, i.e. 21.2±0.3 (N=43) for 15-19 yrs, 22.7±0.3 (N=146) for 20-29 yrs, 22.4±0.5 (N=52) for 30-39 yrs (All P<0.001).

g) Relation between lifestyle-related diseases and birth weight or gestational age

When birth weight in TS with single compli-
cation of lifestyle-related disease was compared with the cases without any of these complications (2,726.8±24.6 g), it was lower in cases with hypertension (2,609.3±76.6, N=31, P<0.05), dyslipidemia (2,617.2±46.5, N=76, P<0.05), and liver dysfunction (2,579.4±68.6, N=47, P<0.05), while not with diabetes mellitus (2,672.1±97.9, N=23, P=0.45). The data of birth height from the database of FGS was few, and statistical analysis was difficult. Regarding to gestational ages, no difference was observed between cases without any complication (39.0±0.1 weeks, N=247) and cases with single complication (diabetes: 39.3±0.4, N=22, hypertension: 39.2±0.2, N=31, dyslipidemia: 38.9±0.2, N=74, liver dysfunction: 39.0±0.3, N=47) (P=NS, compared to cases without complication).

**h) Relation between karyotype and BMI or lifestyle-related disease**

In chromosomal analysis in 492 cases, 45,X monosomy was found in 142 cases (28.9%), 45,X/46,X,Xi in 83 (16.9%), 46,X,Xi in 45 (9.1%), 45,X/46,XX in 31 (6.3%), other mosaics including 45,X in 147 (29.9%), and the others in 44 (8.9%). The 45,X was the most common karyotype.

Regarding the relation between karyotype and BMI or lifestyle-related diseases, 45,X/46,X,Xi was significantly fewer in diabetic cases compared with other cases (1/24 versus 72/440, P<0.05). However, no association was found between karyotype and cases with a BMI of ≥25 kg/m², hypertension, dyslipidemia or liver dysfunction.

**Discussion**

On a global scale, recent TS cases have been a trend toward obesity, in which the BMI, total fat mass, and visceral fat levels are high and the muscle mass is low [8].

All patients with TS in this study has previously treated with human GH (hGH), and we must take into consideration the possible effect of GH on BMI, since GH decreases adipose tissue. However, it is reported that hGH treatment did not affect any changes on age-related BMI increase in a large number of TS (2,468 cases under 20 yrs old) compared with non-treated women with TS [9].

In our study, BMI level and prevalence of obesity in TS were significantly higher than those of general female population in each age group between 15 and 39 years. However, an increase in BMI with age was not observed in TS. This finding indicates that women with TS tend to become obese from young ages. The overall mean BMI in cases aged 20 years or older in this study was 23.0 kg/m², which is similar to that of recently reported value of TS women (mean age of 20.4 years) [10]. However, compared with the mean value of 26.2 kg/m² reported by Freriks et al., who studied about 150 cases of TS (mean age of 31 years) [11], the mean value in our study is much lower. Moreover, the proportions of cases with a BMI of ≥25 and ≥30 in their study were 52.7% and 20.7% respectively, which is much higher than those in our study.

Women with TS had no tendency toward obesity when Henry Turner first described 7 cases, their mean BMI calculated by us from their height and body weight was 18.4 kg/m² (range 13.9-20.8) [12]. There was no obesity; only underweight in all cases. Over the past 40 years, the frequencies of preobese and obesity have increased dramatically in all age ranges in the US and other countries [13]. According to a study based on data from the US National Health and Nutrition Examination Survey (NAHNES), the proportion of females aged 20–39 years with a BMI of ≥25 was 54.5%, whereas it was 10.3% in Japan [6]. According to the study in US, overweight in women aged 19 or younger (children and adolescents) was found in 15.1%, whereas the proportion in Japan was 3.8%. In the US, the tendency toward obesity can be seen from childhood [14]. In Japan, although women with TS tend to be obese more often than the general female population, the severity is mild in comparison with the Netherlands, as mentioned earlier. In addition to reduced physical activity and a sedentary lifestyle, which are often seen in TS [3, 4], it is thought to be due to the tendency toward an increase in body weight with trend of times (secular trend) caused by changes in the social environment and other factors including food culture and vehicular transport, which differ among countries. Underweight was found in 8.1% of our cases. Anorexia nervosa has been reported as a complication in TS [15]. The fact that 7 TS cases reported by Henry Turner, mentioned above, was not obese indicates that even though patients with TS tend to become obese by constitution, the body weight is controllable. The prevalence of diabetes in TS was higher than in the Japanese general female population. Diabetes was found in 5.4% of all TS, which was apparently less than in adult TS reported from over-
seas in the past (10–25%) [16, 17]. This is presumably related to the different Japanese social environment and the lower proportion of severe obesity than other countries. Generally, diabetes is a serious disease accompanying obesity [18]. In this survey, the BMI levels in TS patients with diabetes were significantly higher than those without diabetes. The prevalence of diabetes increased with increasing BMI.

The prevalence of hypertension in women with TS was higher than in the Japanese general female population. However, the prevalence seen in adult TS women (8.5%) was much lower than the rates in adult TS (24–40%) reported in the past [1, 8, 19-21]. Generally, obesity is associated with hypertension [22, 23]. In this study, BMI levels in TS women with hypertension were significantly higher than in those without hypertension and the prevalence increased with increasing BMI. Only few TS cases of hypertension, even early-onset hypertension, are attributable to renal disease or coarctation of the aorta and the cause in the majority of cases is not known clearly [1]. However, it is reasonable to infer that obesity in TS is associated with hypertension.

The prevalence of dyslipidemia in adult TS women was higher than that in the general female population in Japan [8]. While prevalence of dyslipidemia in our study population was 18.9%, to date, conflicting results on dyslipidemia in adults TS women have been reported [1, 2, 11]. However, many recent reports have noted the complications, such as increased LDL cholesterol, triglycerides and reduced LDL particle size, which can cause atherosclerosis [4, 24]. Generally, dyslipidemia is strongly associated with obesity, particularly in visceral fat type obesity. The mean BMI in TS women with dyslipidemia was significantly higher than in those without dyslipidemia and the prevalence of dyslipidemia increased with increasing BMI. These findings indicate that obesity is strongly associated with dyslipidemia in TS.

Adult TS women have higher prevalence of liver dysfunction than Japanese general female population. So far, there are many reports of TS women with liver dysfunction [4, 17]. Sylven et al. stated that γ-GTP levels are elevated in TS and 80% or more cases have abnormalities in one of the hepatic enzymes [25]. In this study, TS women with liver dysfunction showed significantly higher BMI than those without liver dysfunction and the prevalence rate of liver dysfunction increased with increasing BMI. Thus, obesity may be associated with liver dysfunction in TS and it is probably induced by various pathophysiological mechanisms such as steatosis, steatofibrosis and steatohepatitis [26]. Additionally, BMI levels of TS women with a single complication were significantly higher than those without complications and BMI increased further with the number of complications. BMI of patients with either three complications was significantly higher than that of those with either two or one complication. The highest BMI value was found in cases with combination of hypertension, diabetes and dyslipidemia. Interestingly, although BMI in TS without these diseases was within the normal range, it was significantly higher than those in the general female population.

It is well known that early fetal malnutrition promoting adult obesity and predispose to metabolic syndrome [9]. Therefore, we have examined the relationship between birth weight and gestational ages of TS as these subjects frequently delivers with low birth weight and length [27].

While there were no differences in gestational ages between TS women without any complication and subjects with single complication, mean birth weight was lower in the latter. This may imply that lifestyle-related disease in TS today are closely related to increased BMI due to less active daily life and social environment mentioned above, and such BMI might be already programmed at fetal stage [9, 28].

Although there is a report that the proportion of 46,X,Xi is high in TS cases with diabetes [17], we did not see such association and rather found a significantly smaller proportion of 45,X/46,X,Xi in diabetic cases, although the reason is not known.

No specific association was found between the karyotypes and BMI, hypertension, dyslipidemia or liver dysfunction.

In conclusion, the correlation between lifestyle-related diseases and BMI in this study indicates a strong link between TS and obesity. Since prevalence of these diseases seemed higher in our TS population than in the general female population, TS women are considered to be a high-risk group for lifestyle-related disease. For obese TS women it is important they be given nutritional instruction and exercise therapy to control their body weight to prevent or alleviate these diseases. No constant relationship was found between obesity (BMI ≥25), lifestyle-related diseases and karyotypes.
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Disclosure

The authors have no potential conflict of interest to declare.

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