

## DESCRIBING LYMPHEDEMA IN FEMALES WITH TURNER SYNDROME

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### ABSTRACT

*Turner syndrome (TS) is a chromosomal condition affecting an estimated 1 in 2,500 girls where the second X chromosome is missing, or partially formed. This abnormality affects multiple body systems and can lead to short stature, cardiac, neural, and renal abnormalities. Due to the chronic, non-life threatening nature of lymphedema in comparison to other symptoms of TS, it is often ignored by girls and women with TS and their physicians. Consequently, little is known about how lymphedema affects girls and women with TS across the lifespan. Therefore, the objective of the study was to deliver an online survey for females with TS and caregivers in the US, UK, and Canada to provide a worldwide perspective on their current experience with lymphedema within the spectrum of TS. There were 219 participants who completed the survey, and we were able to identify incidence and characteristics of lymphedema across the lifespan. In addition, we found that females with 45,X karyotyping were more likely to report lymphedema symptoms. Lymphedema is not the most significant concern of females with TS, but education, physician evaluation, and assistance with referrals for treatment and management would improve the ease of managing lymphedema in girls and women with TS.*

**Keywords:** Turner syndrome, genetic karyotyping, phenotypes, quality of life, primary lymphedema, age groups

Turner syndrome (TS) is a genetic disorder in females where one of the X chromosomes is missing or structurally abnormal. It occurs in 1 in 2500-3000 live births, and presents with a variety of characteristics (1). The feature most commonly associated with TS is short stature, but there are many other body systems that are affected by the malformation or absence of an X chromosome, including cardiac abnormalities, ovarian dysgenesis, ocular symptoms, hearing disorders, renal dysfunction, skin disorders, delayed growth pattern, abnormal orthopedic development, IQ and attention deficits, and swelling/edema/primary lymphedema (2).

While edema/lymphedema is only one characteristic of TS, and may not require immediate attention in comparison to serious cardiovascular defects, edema can progress to lymphedema, which is progressive in nature and can create unnecessary complications such as recurrent infection and progressive skin changes if left untreated (3-5). This issue is compounded by the fact that despite the suspected correlation between fetal edema and multiple system involvement, some TS patients do not present with edema at any time in their life, especially those with mosaic monosomy. Females with TS can be born

with edema in hands and/or feet which can be one of the first indications to medical providers to check for karyotype chromosomal abnormalities (1).

Primary lymphedema is described as a developmental disorder of the lymphatic vessels and/or the lymph nodes, which can be present at birth, or can occur later in life in contrast to secondary lymphedema which occurs as a result of known damage to the lymphatic system such as cancer or surgery (5). A study completed in 2013 by Blome et al, found the average time span between first symptoms of edema and ultimate primary lymphedema treatment was 13.7 years as opposed to an average of 1.7 years for secondary lymphedema patients (6). Individuals with TS are included in the primary lymphedema category, due to fetal lymphatic abnormalities resulting in a variety of manifestations across the lifespan (3,7-9).

Studies utilizing imaging of the lymphatic system (lymphoscintigraphy) highlight the challenge with identifying edema/lymphedema in individuals with TS. For example, Bellini et al performed lymphoscintigraphy on 18 females with TS, 15 of which demonstrated a defective lymphatic system. Of these 15 females, 11 showed no signs of outward edema/lymphedema, which is significant as TS patients may be at risk for developing complications associated with lymphedema without realizing they are at risk (10). Furthermore, results from a survey distributed at the National Turner's Syndrome Conference in England indicated that 57% of the sample reported experiencing lymphedema; however, of the 200 questionnaires disseminated, only 74 were returned, leading the author to recommend further research be completed with a larger and broader sample to better understand lymphedema in the population (11).

Therefore, the purpose of this study was to disseminate a web-based survey to identify the incidence, demographic characteristics, physical and psychosocial effects, knowledge level of individuals, and treatment approaches

to lymphedema in girls and women with TS across the lifespan.

## *METHODS*

### *Participants and Procedures*

IRB approval was obtained to ensure that all procedures were considered ethical. A survey cover letter was made available on the first screen on the survey followed by study eligibility criteria, which were presented via yes/no question. Specifically, respondents were included if they answered "yes" to either (1) being a female who is 13 years of age or older and is diagnosed with Turner Syndrome or (2) a family member/caregiver of a female diagnosed with Turner Syndrome. If the respondent answered "no" they were directed to the end of the survey. The survey was anonymous, and no identifying information was collected.

We administered an observational, cross-sectional web-based survey in a HIPAA compliant tool. Based on a comprehensive literature review and observation with qualitative feedback from females with TS and their caregivers, we developed a set of survey questions to gather information regarding swelling/lymphedema across the lifespan for TS patients. A panel comprised of women with TS, caregivers of TS minors, and experts provided feedback for the final survey. The online survey was distributed via email and social media by the Turner Syndrome Societies of the US, UK, and Canada. Flyers with the web link were also distributed at the 2014 National Turner Syndrome Society US Conference in Jacksonville, FL.

The first part of the survey included demographic questions and information about the subject's Turner Syndrome history and symptoms. Towards the middle of the survey, a question asked whether the subject has ever experienced swelling of their arms or legs. If the subject answered "no," then they were directed to the end of the survey.

**TABLE 1**  
**Demographic Information**

	0-24 years old	25-44 years old	45 years old or older	Total
<b>Age</b>	100	104	15	219
<b>Race</b>				
Am. Indian/Alaska Native	3 (3%)	0 (0%)	0 (0%)	3
Native Hawaiian/Pacific Islander	1 (1%)	1 (1%)	0 (0%)	2
Black/African American	1 (1%)	0 (0%)	0 (0%)	1
White, Non-Hispanic	86 (86%)	66 (86%)	41 (98%)	193
Hispanic, Latino, Mexican Am.	6 (6%)	8 (10%)	1 (2%)	15
Other	3 (3%)	1 (1%)	0 (0%)	4
<b>Location</b>				
United States	67 (67%)	43 (56%)	23 (55%)	133
United Kingdom	24 (24%)	14 (18%)	13 (31%)	51
Canada	5 (5%)	11 (14%)	6 (14%)	22
Australia	1 (1%)	3 (4%)	0 (0%)	4
Other	3 (3%)	6 (8%)	0 (0%)	9
<b>Setting</b>				
Urban	69 (69%)	53 (69%)	28 (67%)	150
Rural	31 (31%)	24 (31%)	14 (33%)	69
<b>Education Level</b>				
Never attended through Kindergarten	19 (19%)	0 (0%)	0 (0%)	19
Elementary school through middle school	40 (40%)	1 (1%)	0 (0%)	41
Some high school	19 (19%)	1 (1%)	1 (2%)	21
High school graduate or GED	3 (3%)	6 (8%)	3 (7%)	12
Some college or technical school	8 (8%)	12 (16%)	14 (33%)	34
College graduate or higher	11 (11%)	57 (74%)	24 (57%)	92
<b>Lives with</b>				
Alone	1 (1%)	23 (30%)	13 (31%)	37
Parents	90 (90%)	17 (22%)	3 (5%)	110
Spouse	3 (3%)	30 (39%)	22 (52%)	55
Siblings	0 (0%)	2 (3%)	1 (2%)	3
Other relatives	1 (1%)	0 (0%)	1 (2%)	2
Significant other	0 (0%)	1 (1%)	3 (7%)	4
Friends	4 (4%)	4 (5%)	0 (0%)	8
Caregiver	1 (1%)	0 (0%)	0 (0%)	1

If they answered “yes,” then they continued with questions asking about swelling and lymphedema.

The Lymphedema Life Impact Scale (LLIS) was included in the survey and asked participants to rate the severity of different categories related to function and symptoms of lymphedema. The severity of symptoms was calculated to translate into percent impairment (12).

#### *Data Analysis*

Survey results were summarized using

appropriate descriptive statistics including means and standard deviations or medians and ranges for quantitative variables, and counts and percentages for categorical variables. The data were stratified into three categories based on age: (1) before birth to 24 years old; (2) 25 to 44 years old; and (3) 45 years or older. Girls and young adults between ages 0 and 24 were grouped together in the “younger” category to account for those individuals who may still be under the care of their parents/guardians. Women between 25 and 44 years old were grouped together in the “middle” category to account

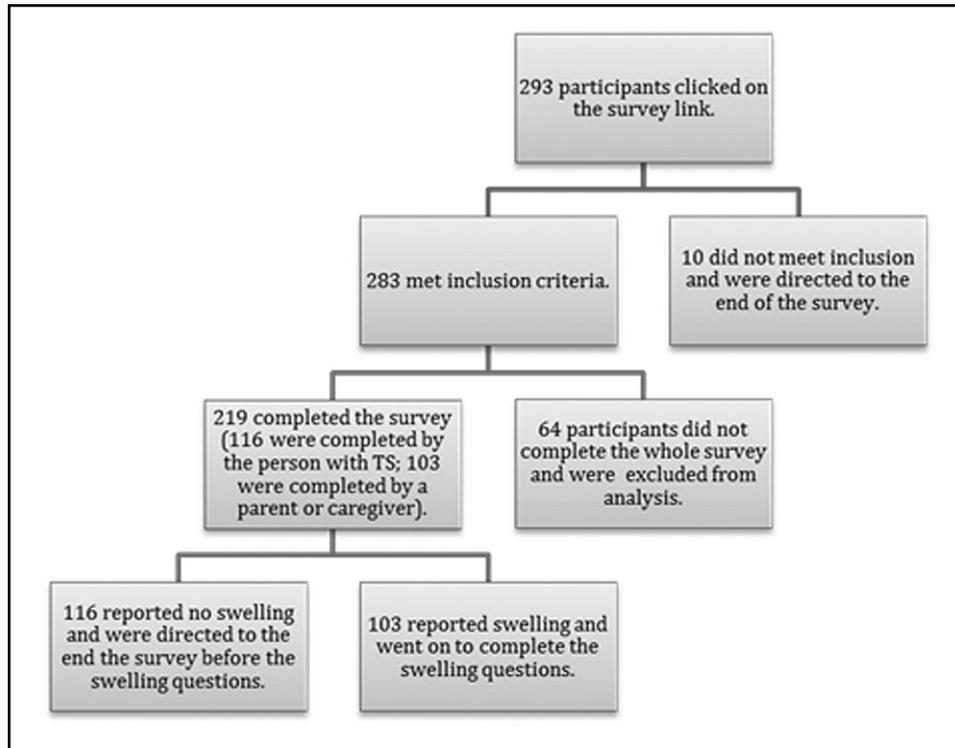


Fig. 1. Eligibility

for individuals' early and middle adult experience. 45 and older were grouped in the "late" category to capture middle and late adulthood. These categories were further analyzed between those who reported having experienced swelling and those who did not. Chi-square or Fisher's exact tests were used to analyze the categorical variables, and t-tests were used for the quantitative variables.

## RESULTS

Data were analyzed in three groups: individuals with TS aged 0-24, 25-44 and 45 or older. Demographic results and eligibility results are displayed in *Table 1* and *Fig. 1*, respectively. Genetic karyotyping of respondents is displayed in *Table 2* according to age group and occurrence of swelling. The people who responded "other" or "don't know" regarding their genetic karyotyping were excluded from this table to accurately identify

those with a formal diagnosis. A comparison of symptoms reported between karyotypes is displayed in *Table 3*.

### Participants aged 24 or younger (younger group)

#### *TS History*

100 of the 219 participants (46%) were included in this younger age group. 61% were under 12 years old; 22% between 13 and 17 years old; and 17% between 18 and 24 years old. 82% of the surveys were completed by a parent or caregiver in this group. The majority in this age group were diagnosed with TS within the first year (59%). 12% were diagnosed between 12 months and 5 years old; 22% between 6 and 12 years old; and 6% between 13 and 18 years old. Only one person did not know when they were diagnosed.

95% of participants reported following

**TABLE 2**  
**Genetic Karyotyping and Swelling Occurrence**  
**by Age Group**

<b>Karyotype</b>	<b>45,X</b>	<b>Mosaic Monosomy X</b>	<b>p-value</b>
<b>24 and under</b>			
Swelling anytime	27 (52%)	3 (17%)	0.0092
Never had Swelling	25 (48%)	15 (83%)	0.0092
<b>25-44</b>			
Swelling anytime	20 (53%)	3 (18%)	0.0151
Never had Swelling	18 (47%)	14 (82%)	0.0151
<b>45 and older</b>			
Swelling anytime	8 (67%)	6 (38%)	0.1266
Never had Swelling	4 (33%)	10 (63%)	0.1266

**TABLE 3**  
**Comparing Symptoms Between Karyotypes**

<b>Symptom</b>	<b>45,X</b>	<b>Mosaic Monosomy X</b>	<b>p-value</b>
Short stature	100 (96%)	46 (88%)	0.0644
Heart problems	54 (52%)	20 (38%)	0.1125
Kidney problems	25 (24%)	8 (15%)	0.2122
High blood pressure	33 (32%)	10 (19%)	0.0995
Ear/hearing problems	62 (60%)	27 (52%)	0.3602
Low set ears	49 (47%)	9 (17%)	0.0003
Speech problems	22 (21%)	6 (12%)	0.1401
Vision problems	43 (41%)	10 (19%)	0.0060
Dental problems	39 (38%)	8 (15%)	0.0045
Obesity	18 (17%)	10 (19%)	0.7680
Swelling of hands and feet	68 (65%)	10 (19%)	<.0001
Webbed neck	42 (40%)	5 (10%)	<.0001
Learning differences	56 (54%)	18 (35%)	0.0234
Gluten intolerance	6 (6%)	5 (10%)	0.3764
Toenail problems	35 (34%)	14 (27%)	0.3932
Abnormal sexual organ development	18 (17%)	18 (35%)	0.0156
LLIS Percent Impairment, median (Q1-Q3)	14.7 (5.9-25.0)	4.4 (0-11.8)	0.0255

**TABLE 4**  
**Comparison of Turner Syndrome Symptoms and Skin Changes Across Age Groups**

	Age Group			p-value
	24 or younger	25-44	45 or older	
<b>Symptoms</b>				
Short stature	91 (91%)	70 (91%)	40 (95%)	0.6624
Heart problems	49 (49%)	31 (40%)	12 (29%)	0.0737
Kidney problems	24 (24%)	18 (23%)	5 (12%)	0.2435
High blood pressure	22 (22%)	18 (23%)	23 (55%)	0.0002
Ear/hearing problems	49 (49%)	46 (60%)	32 (76%)	0.0104
Low set ears	46 (46%)	25 (32%)	11 (26%)	0.0448
Speech problems	29 (29%)	9 (12%)	3 (7%)	0.0014
Vision problems	35 (35%)	27 (35%)	14 (33%)	0.9787
Dental problems	38 (38%)	22 (29%)	5 (12%)	0.0077
Obesity	12 (12%)	26 (34%)	12 (29%)	0.0018
Swelling of hands and feet	46 (46%)	41 (53%)	20 (48%)	0.6231
Webbed neck	31 (31%)	21 (27%)	11 (26%)	0.7932
Learning differences	53 (53%)	25 (32%)	11 (26%)	0.0024
Gluten intolerance	9 (9%)	7 (9%)	3 (7%)	0.9256
Toenail problems	39 (39%)	23 (30%)	10 (24%)	0.1670
Abnormal sexual organ development	13 (13%)	24 (31%)	13 (31%)	0.0064
<b>Skin changes</b>				
None	42 (42%)	32 (42%)	12 (29%)	0.2869
Dry, scaly skin	34 (34%)	39 (51%)	26 (62%)	0.0047
Nail problems	35 (35%)	16 (21%)	15 (36%)	0.0843
Abnormal skin color	10 (10%)	3 (4%)	4 (10%)	0.2881
Skin firmness	3 (3%)	3 (4%)	3 (7%)	0.5466
<b>LLIS Percent Impairment</b>	<b>16.4±20.2</b>	<b>26.4±24.3</b>	<b>15.3±17.2</b>	<b>0.0582</b>

up with a physician at least once per year with 85% reporting multiple visits. Areas of evaluation were broad with growth (86%) and heart issues (77%) being the most frequent reason for visit, followed by hearing deficits (60%), female hormones (60%), kidney function (41%), skin issues (31%), lymphedema (29%) and foot/toenail issues (22%). The younger individuals also reported higher priority with learning issues (35%) and psychosocial issues (24%) than did the other two age groups.

The six most common symptoms reported include short stature (91%), learning differences (53%), heart problems (49%), ear/hearing problems (49%), low set ears (46%) and swelling of hands and feet (46%). Participants who reported swelling issues were significantly more likely to report

kidney problems ( $p=0.0170$ ), ear/hearing problems ( $p=0.0361$ ), low set ears ( $p=0.0002$ ), vision problems ( $p=0.0086$ ), dental problems ( $p=0.0119$ ), webbed neck ( $p=0.0026$ ), and toenail problems ( $p<0.0001$ ). Participants who reported no swelling issues were significantly more likely to report gluten intolerance ( $p=0.0420$ ).

Skin changes were reported in 58% of participants and included nail problems (35%), dry, scaly skin (34%), abnormal skin color (10%) and skin firmness (3%) (Table 4). If they had experienced swelling, they were significantly more likely to report dry, scaly skin ( $p=0.0178$ ) and nail problems ( $p<0.0001$ ). Participants who had never experienced swelling were significantly less likely to report skin problems ( $p=0.0003$ ). 17% reported having at least one arm or leg infection by age 24.

73% of participants had used growth hormone (GH). Only 2% of those reported swelling after use, and 17% did not know if GH led to swelling as a side effect. However, those that used GH were significantly more likely to report swelling ( $p=0.0055$ ). 30% of females in this age group tried hormone replacement therapy (HRT). No one reported swelling after HRT use, and 9% were unsure if swelling occurred after use.

### *Swelling History*

At this section of the survey, participants were asked if they had ever had swelling in any of their arms or legs in their lifetime. 36 participants reported having swelling in their arms or legs and 5 did not know. Those that did report swelling and those that did not know if they had swelling were both directed to complete the remainder of the survey which pertained specifically to swelling. The 59% that reported never having swelling were directed to the end of the survey and their participation was complete.

For the 41 individuals who continued to the swelling portion of the survey, 86% reported first noticing it within the first year of life, and 73% of these individuals had swelling in both hands and feet at birth. Swelling went away for 39% of participants but remained for 51%. If the swelling did go away, it did so within the first four years of life and did not usually return for these individuals.

### *Lymphedema Knowledge and Diagnosis*

Participants in the younger age group knew more about lymphedema than the 25-44 and >45 age groups. The three most cited areas of knowledge included cause (54%), treatment (44%) and need for compression wear (39%). However, of all participants, 32% knew nothing about lymphedema. Individuals indicated that they learned about lymphedema from the internet (51%), doctor (39%), TS information pamphlets (27%) or lymphedema therapist (27%).

Based on images presented in the survey, participants self-rated their swelling across the spectrum with Stage 0 at 22%, Stage 1 at 29%, Stage 2 at 34% and Stage III at 15%.

Of the participants who reported swelling, 63% were diagnosed with lymphedema by a clinician, and of those, 88% were diagnosed within the first year of their life.

### *LLIS*

### *Lymphedema Coping and Treatment*

The three most frequent coping strategies for lymphedema were talking to friends and family (44%), ignoring swelling and proceeding with normal activities (32%) and talking to a lymphedema therapist (24%). Prayer was a significant coping mechanism ( $p=0.0427$ ) for individuals who were never formally diagnosed with lymphedema.

Three areas that individuals reported having issues due to lymphedema included trouble finding shoes that fit and are aesthetically pleasing (68%), appearance (51%) and wearing compression stockings (27%).

Individuals reported physicians typically did not recommend immediate action (37%) for swelling/lymphedema issues, and 20% indicated physicians did not seem to include swelling/lymphedema in their evaluation. If lymphedema was addressed, 29% reported they were referred to lymphedema treatment centers/therapists. Of those diagnosed with lymphedema, 59% had their diagnosis within their first year of life, although only 29% reported receiving treatment within that year. In addition, 51% of participants reported never receiving any treatment for their lymphedema while 32% did not know that treatment for swelling existed. Most people who were treated (32%) traveled less than an hour to their appointment ( $p=0.0179$ ). Of those treated, 39% received a doctor's referral to a lymphedema therapy center or therapist.

Of those diagnosed with lymphedema, 38% ( $p=0.0067$ ) reported wearing compression garments, which the majority (38%) got from

a lymphedema therapist ( $p=0.0067$ ). The primary reason people reported not wearing compression garments was because they did not think they were needed (46%).

### Ages 25 - 44

#### *TS History*

77 respondents completed the survey in the 25-44 year old age group; 22% of the respondents were caregivers. 35 participants (45%) were between the ages of 25 and 34, and 42 participants (55%) were between 35 and 44. While the majority of individuals in this age group were diagnosed in the first year of life (46%), an equal number of respondents were diagnosed in childhood and adolescence (46%). 4 respondents were diagnosed between the ages of 19 and 35, and 2 respondents were diagnosed between the ages of 36 and 55 years old.

82% of respondents reported following up with a physician at least once per year, with 44% reporting multiple visits and only 10% reporting no visits. The 3 primary areas evaluated by physicians during the visit included hormones (66%), heart function (62%) and kidney function (36%). The main symptoms reported included short stature (91%), ear/hearing problems (60%), swelling of hands and feet (53%), heart problems (40%) and vision problems (35%). Participants who reported that they had swelling were significantly more likely to report low set ears ( $p=0.0003$ ), dental problems ( $p=0.0300$ ), obesity ( $p=0.0098$ ), and webbed neck ( $p=0.0061$ ).

Regarding skin changes, 51% reported experiencing dry, scaly skin, 21% reported nail problems, 4% reported abnormal skin color and 4% skin firmness. Of note, 18% reported experiencing an arm or leg infection at least once in their lifetime.

62% of respondents reported using GH therapy, and 49% did not think that it caused swelling in their limbs, while 3% believed it was a direct cause and 12% were unsure. 69%

of participants in this age group reported trying HRT, and again, half (53%) did not think it caused swelling in their limbs, with only 4% believing it did cause swelling (15% were unsure).

#### *Swelling History*

At this point of the survey, participants were asked if they have ever experienced swelling in their arms or legs. If they had not, they were directed to the end of the survey. 37 participants reported experiencing swelling and one did not know, for a combined total of 38 that completed the set of questions related to swelling experience.

The majority of individuals first reported noticing swelling within the first year of life ( $n=22$  respondents; 58%), while 4 noticed in late childhood/early adolescence, and 9 in adulthood. 45% of participants who were born with swelling had it in both hands and feet while 21% did not know where swelling was present at birth. Swelling resolved for the majority of participants who were born with swelling (37%) but remained present for 42%. For participants whose swelling resolved, it was more likely to resolve within the first four years of life (29%).

For most participants (87%), swelling returned at some point in their life. A few people identified that it returned after trauma to the limb (16%) or with weight gain (11%) whereas the majority (45%) could not identify a trigger event. For participants whose swelling returned, it was more likely to return between ages 19-35 (32%). 29% of respondents did not know how old they were when swelling returned.

#### *Lymphedema Knowledge and Diagnosis*

15 respondents (39%) did not know anything about lymphedema; 39% understood the cause; 37% understood the need for compression wear; 29% understood the need for reducing risk of complications; and 32% understood the importance of stopping its

progression. The majority of participants learned about lymphedema from their doctor (37%) or the internet (34%) although 32% reported never learning about lymphedema.

When shown pictures of the stages of swelling, 8% of participants reported their swelling at Stage 0, 53% Stage 1, 34% Stage 2, and 5% Stage 3. Swelling was formally diagnosed as lymphedema for 20 participants (53%). Of those participants, the majority were diagnosed in the first year of life (60%).

## LLIS

### *Lymphedema Coping and Treatment*

When asked how they coped with their feelings about swelling/lymphedema 61% reported ignoring their swelling and proceeded with normal activities. 32% talked about their swelling with friends or family and 24% avoided thinking about it. 63% did not like the appearance of swelling, and 61% reported having trouble finding shoes that fit and were aesthetically pleasing. Finally, 42% reported pain/discomfort from the swelling.

39% of individuals reported that physicians did not include swelling in their evaluation and of those that did 29% did not recommend immediate action. Furthermore, 34% of respondents indicated that swelling had never been addressed with their physician and 61% of those who have swelling had not yet received treatment for it. The most reported reason for not receiving treatment was not knowing they could receive treatment (39%). However, 32% reported having swelling addressed within the first year of diagnosis and 21% of doctors referred patients to lymphedema treatment centers or therapists. 12 of the 15 participants who reported receiving treatment drove less than an hour to receive it.

79% of participants reported not wearing compression garments to help with their swelling because they did not like wearing them (29%), or didn't think they were needed (26%). Those who do wear compression

garments were likely to purchase them at a store (24%).

### Ages 45 and older

#### *TS History*

The 45 and over group had the fewest participants with 42 responses, of which 4 were caregivers. 27 (64%) were 45-54 (29%) years of age, 12 (7%) were 55-64 years of age and 3 were 65-74 years of age. 23% of participants were diagnosed between 0-5 years, 62% between 6-18 year, and 14% in adulthood.

81% of participants visit a physician at least once a year with 36% visiting their physician multiple times, and 12% reporting no visits. The most common areas evaluated by a physician were heart function (76%), kidney function (52%), hormones (50%), and hearing (43%). Symptoms reported included short stature (95%), ear/hearing problems (76%), high blood pressure (55%), swelling of hands and feet (48%) and vision problems (33%).

Skin changes that were noticed included dry, scaly skin (62%), nail problems (36%), abnormal skin color (10%), and skin firmness (7%). 12 participants (29%) reported no skin changes. Notably, 26% reported having an arm or leg infection at least once in their lifetime.

Only 10 respondents (24%) reported ever using GH, and no responses indicated that it may have contributed to swelling. Most respondents (90%) had tried HRT, and 3 (7%) felt that it may have contributed to swelling in their limbs; 9 respondents (21%) were not sure.

#### *Swelling History*

At this point in the survey, respondents were asked to report if they had ever experienced swelling in their arms or legs. If they had not, they were directed to the end of the survey. 24 respondents reported experiencing swelling in their lifetime, and they completed the remainder of the survey related to swelling.

Of the 24 respondents who had reported

having experienced swelling, 46% reported that it occurred within the first year of life. The rest of the respondents (41%) reported swelling in adulthood; 13% did not know when it first occurred. 33% of the participants born with swelling knew it was present in both their hands and feet at birth. Swelling went away within the first year of the person's life for 7 of the 13 participants who reported swelling. Swelling did return for many of the participants (54%) but the cause for return was not clear.

### *Lymphedema Knowledge and Diagnosis*

54% of respondents reported knowing nothing about lymphedema, 33% knew the cause of lymphedema and 25% of the need to wear compression garments. 42% of participants in this age group received their information from a physician (42%) or Turner syndrome organization (21%). 38% in this age group had their swelling diagnosed as lymphedema by a physician, but there was not a trend that identified the age at which they were diagnosed.

When shown pictures of the stages of swelling, 8% of participants reported their swelling at Stage 0, 63% Stage 1, 25% Stage 2, and no participants at Stage 3.

### *Lymphedema Coping and Treatment*

Half of the group indicated that they ignore swelling and proceed with normal activities. Humor (33%), Prayer (29%) and Avoidance thinking about it (25%) were also leading coping mechanisms. When asked what bothered them most about swelling/lymphedema, responses were appearance (75%), pain/discomfort (50%) and wearing compression stockings (33%).

Participants were then asked how their physician has addressed their swelling/lymphedema. 42% reported that it was not included in their medical evaluation, 42% reported that no information was provided, and/or 33% that no immediate action was

recommended. 17% of participants also responded that they were referred to a lymphedema treatment center or therapist, and 8% were given information about swelling/lymphedema. 37% of participants who have experienced swelling had been formally diagnosed with lymphedema by a clinician. 7 (29%) discussed the symptoms with their doctor within the first year of noticing swelling, and 2 (8%) waited over 9 years to discuss with their doctor; 7 (29%) have yet to discuss symptoms with their doctor. 7 participants (29%) sought out treatment within the first year of diagnosis, whereas 16 participants (67%) have not yet received treatment. Participants were asked what types of reasons caused a delay in treatment, and 17% said that they did not know it could be treated; 17% did not have a doctor's referral for treatment. Of the 9 who were treated, 6 found their lymphedema center/therapist via doctor referral. Additionally, 5 of the 9 respondents who received treatment drove less than one hour to receive it.

Most respondents (79%) reported not wearing compression stockings primarily because they didn't think they are needed (50%).

Table 5 compares symptoms, skin changes and severity of symptoms (LLIS) across age groups. A significantly higher proportion of 45 and older patients had high blood pressure. We also found that ear/hearing problems and dry, scaly skin increases with age. Low set ears, speech problems, dental problems, and learning difficulties all decrease with age. Other significant findings were that obesity was most prevalent in the middle age group, and abnormal sexual organ development was significantly higher in the middle and older aged groups. Although not significant, the persons in the middle age group trended toward experiencing a greater severity of symptoms based on the LLIS.

### *DISCUSSION*

**TABLE 5**  
**Comparison of Swelling Based on Growth Hormone Use by Karyotype**

	<b>GH &amp; Swelling</b>	<b>no GH &amp; Swelling</b>	<b>p-value</b>
45,X	40 (62%)	15 (41%)	0.0408
mosaic monosomy X	5 (20%)	7 (27%)	0.5601
Don't know	17 (65%)	9 (64%)	0.9446
Other	1 (10%)	3 (30%)	0.5820

The purpose of this study was to accurately describe the lymphedema experience across the life span as reported by girls and women with TS, and also to provide education about lymphedema for them, their caregivers and healthcare providers.

#### *Genetic Karyotyping*

Our results were consistent with Loscalzo's work on linking fetal lymphedema with cardiovascular defects and neck webbing (4). In addition, participants with 45,X karyotype also reported significantly greater incidence of vision, dental, swelling, learning differences, and abnormal sexual development. We also found that these characteristics changed across the lifespan, with decreased reporting of some of the physical and cognitive characteristics (*Tables 3 and 4*). It is possible that these symptoms were addressed earlier in the person's lifetime and were not as important as they aged. Participants with 45,X karyotyping and who have used GH were significantly more likely to report swelling or lymphedema but there was no direct evidence that GH caused swelling, emphasizing the importance of further investigation. In contrast, participants with mosaicism tended to report less expression of TS characteristics across all ages (*Table 5*). Clinically, 45,X karyotypes may have more involvement across all body systems but can vary in presentation of severity of symptoms. An extensive clinical assessment should be

utilized prior to performing lymphedema treatment.

#### *TS History*

The younger group tended to be diagnosed within the first year, whereas the middle group was diagnosed as much in middle childhood as within the first year. Our results indicating that the late group tended to be diagnosed in later childhood could be attributed to advances in technology, prenatal care and increased awareness (13).

In general, most groups followed up with their doctor every year, but the younger group tended to visit with the most frequency, likely due to evolving diagnosis or intervention. Current literature indicates a need for health surveillance across the lifespan for patients with TS (14-17). Most TS medical evaluations included cardiac, kidney, and endocrine functions, with a developmental focus for the younger group. As the ladies aged, increased skin changes, infections, and weight gain occurred indicating the chronic progressive nature of untreated lymphedema (18,19).

The younger group reported the highest percentage of GH use, whereas the older group reported more use of HRT. This is expected because growth is generally addressed before female hormones. However, those that used GH were significantly more likely to report swelling in the younger group, specifically if 45,X was the reported karyotype. While some research links growth hormone use with

lymphedema onset, results from this study were inconclusive (20).

The late group was less likely to receive GH possibly due to being diagnosed at a later age so GH would not have been considered. The older group may not have had ready access to GH or physicians specializing in providing GH at the time and history they would seek it. Even today, the age and of use and duration of GH is controversial (21).

### *Swelling History*

Among all age groups that had experienced swelling, about half knew they had swelling in hands or feet in their first year of life. However, the younger group reported a higher awareness of swelling at birth. The younger group tended to have more support from caregivers, who would be more able to observe, recall, and report swelling at birth.

Roughly 1/3 of the younger and middle group reported that swelling went away by early childhood, which confirms literature that swelling recedes in childhood (1). If swelling doesn't go away by age four, it was likely to remain and not resolve. Due to the low number of participants in the late group, it is difficult to draw a conclusion about their swelling in childhood.

### *Lymphedema Knowledge and Diagnosis*

The younger age group tended to be more knowledgeable than the middle and late groups. It is believed that caregivers are more involved with care in this group, which accounts for more knowledge. However, across the age groups, about 1/3 - 1/2 of participants reported knowing nothing about lymphedema. Knowledge was obtained primarily from doctors and the internet with the young and middle groups, in contrast to the older group who received information from doctors and TS support groups. Despite access to technology, doctors are still the number one resource for learning about lymphedema.

### *LLIS*

The LLIS questionnaire showed that the middle age group tended to experience more severity of their lymphedema symptoms compared to the young and late group. In addition, individuals with 45,X experience statistically significant greater severity of symptoms.

### *Lymphedema Coping and Treatment*

All groups tended to cope with swelling by ignoring symptoms to some extent, with the middle group being most likely to dismiss symptoms. Talking to friends and family or prayer were other coping strategies (22).

All groups were concerned about physical appearance and finding shoes (23). The middle and late group complained of pain and discomfort more prominently. It is suspected that the younger group would have more difficulty finding shoes because they are growing and buying shoes more frequently. Additionally, it is possible pain and discomfort in the older group is reported more frequently because the swelling has been there longer and causes more difficulty, due to the chronic progressive nature of lymphedema (5).

The younger group tended to be more likely to have swelling included in their medical evaluation. For roughly 1/3 of all participants, the doctor did not recommend immediate action. There seemed to be a delay in seeking treatment after being diagnosed with lymphedema, as well (8).

All groups reported not liking to wear compression garments. Of the few who wear compression garments, the younger group tends to be more compliant, possibly because of caregiver support. The middle and late groups tended to report not wearing compression regularly.

### *Limitations*

Because this was an international, online survey, there were likely cultural and language variations that may have influenced

how a person responds to the questions. Some of the questions may have been answered differently based on differences in healthcare delivery systems and access to medical specialties. Additional limitations may include self report, caregiver bias, fewer older participants, and less ethnic diversity.

Another limitation, not related to the methodology, is that swelling/lymphedema in the TS population is not a high priority and tends to be overlooked in light of vital organ system involvement, so it may have not been reported (4,24). TS swelling is not clearly identified as a primary lymphedema as its presentation is included within the syndrome's features (1,24).

### CONCLUSION

Although it is known that TS is linked with impaired lymphatic development, many respondents never report experiencing swelling/lymphedema in their lifetime. In addition, females with 45,X karyotyping are significantly more likely to experience swelling and report increased severity of symptoms. Swelling can present at birth, and if it does not recede by age four, it is likely to be a chronic condition. Swelling assessment should be part of the yearly routine follow up, as complications tend to progress with age. More research is needed to determine the relationship between hormones and swelling. A trigger event for onset of lymphedema could not be identified with our data. Swelling/lymphedema is not the most significant symptom that a TS patient experiences, so it is often ignored, but it can be a chronic, progressive condition if not addressed. Increased physician awareness, education and assistance with referral and treatment are recommended.

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