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# Dermatological concerns for women and girls with Turner syndrome

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DERMATOLOGICAL CONCERNS FOR WOMEN AND GIRLS WITH TURNER SYNDROME

by

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# DERMATOLOGICAL CONCERNS FOR WOMEN AND GIRLS WITH TURNER SYNDROME

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**ABSTRACT**

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Turner syndrome (TS) is associated with distinct manifestations in women and girls involving many mesoderm-derived body systems, including endocrine, cardiovascular, lymphatic, and renal. Many TS signs and symptoms may go undetected until teenage years or later. Non-mesoderm-derived manifestations of dermatological nature, which are just as common as other features of TS, but often present either at birth or soon after, can aid in earlier detection and impact clinical management. The main objective of this study was to determine self-reported prevalence of various dermatological manifestations in a sample of women and girls with TS. We created a six-part questionnaire that included demographic information, dermatology referral experience, impact on quality of life, dermatological manifestation history, special issues in growth hormone therapy, and family history. We analyzed 241 responses from the UTHealth TS registry, TS Society of the United States, and TS social media groups. Although many dermatological concerns present during the first few decades of life, the overwhelming majority of respondents are not provided with dermatology referrals at diagnosis and/or available treatment methods. Some conditions like dry skin, lymphedema, vitiligo, abnormal nails, and history of skin biopsy due to a suspicion for skin cancer were especially predictive of deleterious impact on quality of life. Our data reveal that many skin conditions are highly prevalent in the TS population during the early decades of life and affirm utilizing these conditions in the TS diagnostic process, as well as indicate the need for specialized dermatology referrals to address detrimental quality of life impacts related to skin concerns.

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## BACKGROUND

Turner syndrome (TS) is a common chromosome condition that affects approximately 1 in every 2000 female births. The genetic etiology of Turner syndrome is monosomy X with or without cell-line mosaicism. There are numerous blood karyotypes that are associated with TS; including full monosomy X, mosaic monosomy X, isochromosome, marker chromosome, ring chromosome, partial deletion of one X chromosome, presence of Y chromosome, and isodicentric chromosome (Lin et al., 2019, p. 2002). Most cases involve the paternal sex chromosome. Karyotype-phenotype correlations are typically associated with the percentage of cells that possess one X chromosome—mosaicism. More cell-line mosaicism has been shown to equate to a smaller burden of clinical characteristics related to TS (Lowenstein et al., 2004, p. 775). Those with 45,X and presence of Y chromosome blood karyotypes are more likely to experience lymphedema, autoimmune disease, neuropsychiatric traits, and left-sided heart defects. The presence of Y chromosome material such as with a 45,X/46,XY karyotype introduces separate risks for gonadoblastoma. This risk incurs a recommendation for a gonadectomy (Lin et al., 2019, p. 2002). Karyotype-phenotype correlations elucidate the importance of proper genetic testing to appreciate risk for certain health conditions.

Generally, TS is defined by the presence of distinct clinical features—the most common being short stature and gonadal failure—in a non-ambiguous female with the identification of any sex chromosome abnormalities described above. In addition to these features; abnormalities of the cardiovascular system, renal system, lymphatic system, dentition, behavior, and skin are regularly noted (Lowenstein et al., 2004, p. 769). Both non-mesoderm-derived manifestations are common in TS and can prompt a genetics evaluation, which in turn, can lead to earlier diagnosis of TS (Lee et al., 2014). Most affected body systems in TS have concrete prevalence data and risk evidence for providers to utilize tailored clinical care recommendations. Cardiologists are equipped with information regarding the risk for bicuspid aortic valve (BAV) and aortic coarctation, as well as management guidelines for women with TS. Endocrinologists are provided with guidelines for the utilization of growth hormone (GH) therapy to promote development, puberty induction methods, and special issues with fertility. This trend extends to

specialty physicians such as nephrologists, audiologists, orthodontists, and others (Shankar & Backeljauw, 2017, p. 36). But, while most published clinical care guidelines for TS mention that a referral to dermatology is recommended at diagnosis, clear risk information is not commonly not noted.

In terms of dermatological manifestations associated with TS, common reports are an increased number of melanocytic nevi, primary lymphedema, dysplastic nails, hypertrophic scarring, keloids, vitiligo, and alopecia areata (Lowenstein et al., 2004, p. 769). Large and dysplastic nevi are not commonly reported (Geller et al., 2016, p. 413). The risk for autoimmune disease is 2-3 times the general population risk, including alopecia and non-segmental vitiligo, which is theorized to derive from aberrant X-chromosome inactivation in TS (Goldacre & Seminog, 2013, p. 71). Most literature suggests that the risk of cutaneous melanoma (CM) is not increased for women with TS, despite the manifestation of a risk factor like a high quantity of nevi (Geller et al., 2016, p. 413; Gibbs et al., 2001, p. 1). Furthermore, GH therapy has been suggested to increase the pace of growth of skin nevi, but this notion is not universally accepted (Bourguignon et al., 1993, p. 1505). Nail abnormalities are present in approximately 80% of women with TS. This manifests as small, hyper convex, pitted, or otherwise dysplastic nails (Lowenstein et al., 2004, p. 769). Hypertrophic scarring and/or keloid formation has been hypothesized as increasingly prevalent in the TS population and present in the common locations for TS-related surgeries such as the head, neck, and upper chest (Lowenstein et al., 2004, p. 769). Approximately two-thirds of women report experiencing lymphedema at least one time during their lifespan (Lin et al., 2019, p. 1991). There have been numerous complications reported with lymphedema such as impacted gait, limited dexterity, cellulitis, or trouble dressing (Yüksel et al., 2016). With that, over half of women with TS are estimated to have never tried available treatment options like compression or bandaging (Lin et al., 2019, p. 1991).

The current recommendations for coordinated care for women and girls with Turner syndrome lack tangible information regarding what dermatological inquiries and referrals are appropriate and at what timing throughout the lifespan. Despite the increased prevalence of numerous dermatological findings, there is a lack of guidance for practitioners that care for individuals with Turner syndrome. Moreover, there are currently no studies that investigate the quality of life impact that these common skin

manifestations have on this population. Thus, it is pertinent to further characterize the state of dermatological findings related to Turner syndrome and provide concrete recommendations to guide physicians that care for affected women and girls.

## MATERIALS AND METHODS

### Study design and population

This cross-sectional study was designed and approved under the Institutional Review Board of University of Texas Health Science Center at Houston (HSC-MS-15-0120) to assess self-reported dermatological manifestations, dermatology referral experience, common therapies for select conditions, and quality-of-life impact in women and girls with Turner syndrome at any age.

Our study population included any female with a self-reported clinical or genetic confirmation of Turner syndrome. For respondents who were less than 18 years old surveys were completed by a parent or relative. Our recruitment strategy included contacting the following groups: members of the UTHealth Turner Syndrome Research Registry, members of the Turner Syndrome Society of the United States (TSSUS), and members of Turner syndrome social media outlets (i.e. Facebook groups). Our questionnaire was distributed in three different ways. For the UTHealth registry, members were contacted by both email and phone call to complete our REDCap survey either independently or assisted over the phone. Members of the TSSUS were contacted through the moderated monthly newsletter and social media outlets with an anonymous qualtrics survey link. Facebook group administrators were contacted and consented before posting an anonymous survey link. Surveys distributed to the Facebook groups and TSSUS included exclusionary questions at the start of the survey to identify repeat respondents. Most participants were independent responders with a personal history of TS and 19.41% (n=46) surveys were completed by parents of the person with TS. We received a total of 241 responses and 215 (89%) complete responses.

### Questionnaire design

Our questionnaire was developed after an extensive literature review and consisted of author-designed questions regarding demographic information, referral experience, dermatological

manifestations, treatment plans, and the validated Dermatology Life Quality Index (DLQI). The demographics section included type of respondent (person with TS or parent), age range, ethnicity, and karyotype, if known. The referral experience section queried whether they have ever been referred to see a dermatologist, who referred them, and if they desire a referral now. The quality-of-life scale was a validated 10-point Dermatology Life Quality Index (DLQI). The dermatological manifestations section included inquiries about dry skin, lymphedema, hair loss, dysplastic nails, >20 skin nevi, red marks or patches, skin biopsies, skin cancer, vitiligo, alopecia, keloids, scarring, and acne. All questions if selected "Yes" included additional inquiries about age of manifestation. Some questions if selected "Yes" included additional inquiries about treatment plan, area of body affected, or relevant secondary manifestations. In addition, all participants were asked if they have taken growth hormone and if they have concerns about side effects like increased number of skin nevi, hirsutism, and swelling. Last, each participant was asked to indicate what manifestations asked about in the survey are present in a first-degree relative, as well as write any other concerns they may have outside of those asked in the survey.

**Statistical analysis**

All analyses were performed using Stata v.11. Descriptive analysis was executed for all variables (frequencies, median, and SD, as applicable). For statistical comparisons of significance, Z-test proportion tests, T-tests, Chi-Squared analysis, and Fischer's exact analyses were used with a P value of $< 0.05$. To evaluate the heterogeneity of the data across the three groups, multivariate test of means was completed with a P value of $< 0.05$.

## RESULTS

**Demographics**

Our sample consisted of 191 independent responders (80.59%). The respondents were majority Caucasian with no Hispanic or Latino origin. We observed an age-diverse sample from children aged 0 to 10-years-old to women above 55-years-old (Table 1). Of those who recalled their karyotype (n=165), 45.45% reported 45,X and 15.15% reported 45,X/46,XX. The remaining less common karyotypes were all represented in our sample and can be seen in Table 2.

Table 1. Demographic characteristics

| Age range (n=236) | n (%) | Race (n=234) | n (%) |
|---|---|---|---|
| 0-10 | 2 (0.85%) | American Indian or Alaska Native | 4 (1.71%) |
| 10-14 | 19 (8.05%) | Asian | 3 (1.28%) |
| 14-18 | 14 (5.93%) | Black or African American | 3 (1.28%) |
| 19-24 | 31 (13.14%) | Native Hawaiian or Other Pacific Islander | 0 |
| 25-34 | 45 (19.07%) | White | 216 (92.31%) |
| 35-44 | 52 (22.03%) | Other | 8 (3.42%) |
| 45-54 | 38 (16.10%) | | |
| 55+ | 35 (14.83%) | | |
| **Ethnicity (n=229)** | **n (%)** | **Participant (n=237)** | **n (%)** |
| Hispanic or Latino | 20 (8.73%) | A person with TS | 191 (80.59%) |
| Not Hispanic or Latino | 209 (91.27%) | The parent or guardian of a person with TS | 46 (19.41%) |
| | | Someone else | 0 |

Table 2. Self-reported blood karyotype

| Karyotype (n=165) | n (%) |
|---|---|
| 45,X | 75 (45.45%) |
| 45,X/46,XX | 25 (15.15%) |
| 45,X/46,XY | 4 (2.42%) |
| Deletion Xp | 5 (3.03%) |
| Isochromosome | 10 (6.06%) |
| Mosaic with ring | 15 (9.09%) |
| Mosaic with 47,XXX | 15 (9.09%) |
| Other mosaic with Y chromosome | 5 (3.03%) |
| Something else | 11 (6.67%) |

**Referral experience**

Our sample reported that 149 (63.95%) have been referred to see a dermatologist at some point in their lifetime. Of those respondents; 47 (33.1%) were referred by a medical provider related to Turner syndrome care, 14 (9.79%) were referred at the time of TS diagnosis, and 113 (79.58%) self-identified their dermatological concern. Regardless of referral history, 129 (57.59%) of our sample reported that they are currently concerned about their skin and 52 (23.21%) currently want a dermatology referral (Table 3).

Table 3. Self-reported dermatology referral experience

| Referral status (n=233) | n (%) | Referred by (n=142) | n (%) | Referral timing (n=143) | n (%) |
|---|---|---|---|---|---|
| I have been referred | 149 (63.95%) | My doctor that provides TS care | 47 (33.1%) | At the time of my diagnosis | 6 (4.20%) |
| I have not been referred | 84 (36.05%) | Somebody else | 95 (66.9%) | After a problem came up | 129 (90.21%) |
| | | | | Both | 8 (5.59%) |
| **Who noticed (n=142)** | **n (%)** | **Currently concerned (n=224)** | **n (%)** | **Want referral (n=224)** | **n (%)** |
| My doctor noticed a problem | 29 (20.42%) | I am currently concerned about my skin | 129 (57.59%) | Yes | 52 (23.21%) |
| I noticed a problem | 113 (79.58%) | I am not currently concerned about my skin | 95 (42.41%) | No | 172 (76.79%) |

**Dermatological manifestations**

*Dry, flaky, scaly skin*

One-hundred and seventy-four (78.73%) respondents reported a personal history of dry, flaky, or scaly skin. Of this group, the median age of primary onset was in the second decade of life. Ninety-two (64.79%) of respondents with a history of dry skin also reported a positive family history. See table 4 for complete data on frequency, median age of onset, and positive family history.

*Lymphedema*

Lymphedema was defined as excess fluid collecting in tissues causing swelling. The median age of onset was between birth and two years of age, which is consistent with the natural history of lymphedema in Turner syndrome. Twenty-one respondents (36.80%) reported a positive family history of lymphedema. Family history did not include a separation between primary and secondary lymphedema. Z-test proportion analysis demonstrated a significantly ($z$=170.25, $p<0.05$, 95% CI: 0.30, 0.43) higher prevalence of lymphedema in this sample compared to the reported population prevalence of 0.1%, and a significantly ($z$=-9.26, $p<0.05$, 95% CI: 0.30, 0.43) lower prevalence compared to the estimated 66.66%

(Lin et al., 2019) overall lifetime frequency in TS. Fischer's exact analysis demonstrated an association (95% CI, OR = 35.56, $p<0.05$) between a higher prevalence of lymphedema and 45,X karyotype.

*Hair loss or thinning*

Hair loss was broadly defined as any loss or thinning of the hair, not necessarily resulting in baldness. Eighty-three (37.56%) respondents reported a history of hair loss or thinning of the hair. The median age of onset was within the third decade of life. Of these respondents, 35 (57.37%) reported a family history of hair loss and/or thinning.

*Abnormal nails*

Abnormal nails were defined as small, pitted, abnormally shaped, and/or painful nails. Ninety-five respondents (43.38%) reported abnormal nails. The median age of onset was within the first decade of life. Seventeen (26.56%) reported a positive family history of abnormal nails.

*>20 skin moles*

One-hundred and fifty-four (70.00%) respondents reported the presence of more than 20 skin moles at any point during their lifetime. The median age of onset was within the first decade of life. Seventy-six (59.84%) reported a positive family history of numerous moles. Having more than 20 skin moles were associated with a history of skin biopsy, $X^2$ (1, N=220) = 24.1, OR = 26.61, 95% CI, p=0.00.

*Papules*

Papules were defined as raised red marks and/or patches on the skin, and 89 (40.64%) respondents reported a positive personal history. The median age of onset was within the second decade of life. Twenty-four (36.92%) reported a family history of papules. Papules were associated with a personal history of skin cancer, $X^2$ (1, N=216) = 12.25, OR = 12.38, 95% CI, p=0.00).

*Skin cancer*

Nineteen (8.76%) respondents reported a personal history of skin cancer. Sixteen (84.21%) reported that the affected area was in a sun-exposed area. The most commonly affected body region was the face (n=12, 63.16%). The median age of onset was in the fourth decade of life. Of these individuals, 8 (47.05%) reported a family history of skin cancer. Moreover, 84 (38.18%) individuals reported a history

of at least one skin biopsy due to suspicion for cancer. The median age when they had their first biopsy was in the third decade of life, and 38 (58.46%) also reported that other family members had undergone biopsies due to suspicion for cancer. Z-test proportion analysis showed that this sample's prevalence of skin cancer was significantly lower, ($z$= -4.14, $p<0.05$, 95% CI: 0.05, 0.13) than the general population prevalence of 20% (Stern, 2010, p. 281; *Cancer Facts and Figures 2021*). Notably, 90% (n=17) of those with a history of skin cancer reported having more than 20 skin moles. Pathology reports of biopsied lesions were not available for analysis.

*Vitiligo*

Vitiligo was described as loss of skin coloring in blotches, and 13 (6.05%) reported a positive personal history. The median age of onset was in the second decade of life. Of this sample, 3 (37.50%) reported a family history of vitiligo. Vitiligo was commonly untreated with eight (61.54%) reporting no treatment. The most common treatments implemented were topical medication (n=4, 30.76%) and light therapy (n=2, 15.38%). Z-test proportion analysis demonstrated a significantly ($z$=4.24, $p<0.05$, 95% CI: 0.03, 0.09) higher prevalence of vitiligo between this sample and the general population prevalence of approximately 2% (Krüger & Schallreuter, 2012, p. 1208).

*Alopecia*

Alopecia was defined as sudden hair loss resulting in baldness, and fifteen (7.04%) respondents reported a positive personal history. The median age of onset was in the third decade of life. Of this group, four (40.00%) reported a family history of alopecia. The most common treatments reported were corticosteroid injections (n=6, 40.00%), cosmetic replacements (n=4, 26.67%), and no treatment (n=4, 26.76%). Z-test proportion analysis showed a significantly ($z$=5.24, $p<0.05$, 95% CI: 0.04, 0.10) higher prevalence of alopecia in this sample compared to the general population prevalence, which is estimated at 2% (Mirzoyev et al., 2014, p. 1141; Safavi et al., 1995, p. 630).

*Keloids*

Keloids were described as a raised scar after an injury has healed and 88 (40.93%) of respondents reported a positive personal history. The median age of onset was in the second decade of life. Of this

group, 24 (40.68%) reported a family history of keloids. The most common body regions with keloids were the chest (n=23, 26.14%) and back (n=20, 22.72%). A Z-test proportion analysis showed that this sample had a significantly ($z$=189.41, p<0.05, 95% CI: 0.34, 0.48) higher prevalence of keloids compared to the general population of approximately 0.1% (Sun et al., 2014, p. 805). Fischer's exact analysis demonstrated a statistically significant (95% CI, OR = 19.96, p<0.05) association between a higher prevalence of keloids with both 45,X and 45,X/46,XX karyotypes.

*Abnormal scarring*

Sixty-two (28.70%) of respondents reported a personal history of abnormal scarring and/or delayed wound healing. The median age of onset was within the second decade of life. Of this group,17 (37.78%) reported a positive family history of these concerns.

*Acne*

Sixty-two (28.70%) respondents reported a personal history of acne. The median age of onset was during the second decade of life. Of these individuals, 26 (51.00%) reported a family history of acne. Of those with a history of acne, 46 (74.19%) reported having taken progesterone. Z-test proportion analysis demonstrated significantly ($z$=-14.78, p<0.05, 95% CI: 0.23, 0.35) lower prevalence of acne in this sample compared to the general population prevalence of 73.3% (Safavi et al., 1995, p. 630). See table 4 for complete data on frequency, median age of onset, and positive family history.

Table 4. Self-reported dermatology manifestations

| | **n (%)** | **Median age of onset (age range)** | **Positive family history n (%)** |
|---|---|---|---|
| **Dry skin** | 174 (78.73%)** | 11-20 years old | 92 (64.79%) |
| **Lymphedema** | 73 (33.03%)** | 0-2 years old | 21 (36.80%) |
| **Hair loss** | 83 (37.56%)** | 21-30 years old | 35 (57.37%) |
| **Abnormal nails** | 95 (43.38%) | 0-10 years old | 17 (26.56%) |
| **>20 skin moles** | 154 (70.00%)** | 0-10 years old | 76 (59.84%) |
| **Papules** | 89 (40.64%) | 11-20 years old | 24 (36.92%) |
| **Skin cancer** | 19 (8.76%)** | 31-40 years old | 8 (47.05%) |
| *Have you had a skin biopsy?* | 84 (38.18%) | 21-30 years old | 38 (58.46%) |
| *Was the area sun exposed?* | 16 (84.21%) | | |
| **Vitiligo** | 13 (6.05%)** | 11-20 years old | 3 (37.50%) |

| | | | |
|---|---|---|---|
| **Alopecia** | 15 (7.04%)** | 21-30 years old | 4 (40.00%) |
| **Keloids** | 88 (40.93%)** | 11-20 years old | 24 (40.68%) |
| **Abnormal Scarring** | 62 (28.70%) | 11-20 years old | 17 (37.78%) |
| **Acne** | 62 (28.70%)** | 11-20 years old | 26 (51.00%) |
| *Have you taken progesterone?* | 46 (74.19%) | | |

**p<0.05. *Asterisks represent a significantly different prevalence in the TS sample compared to general population estimates shown by Z-test proportion analysis. For those skin conditions without asterisks, an appropriate general population prevalence could not be estimated and the absence does not imply insignificance.*

**Skin effects of growth hormone (GH) therapy**

Two-thirds (n=144) of our sample reported a personal history of taking growth hormone therapy. Of those, 23.78% (n=34) reported concerns about GH therapy and increased number of skin moles, 19.44% (n=28) about excess hair growth, and 23.78% (n=34) with swelling. Of those with concerns about GH therapy and excess skin moles, 5.88% (n=2) reported a personal history of cancer. Of those with concerns with GH therapy and swelling, 55.88% (n=19) reported a history of lymphedema.

Table 5. Growth hormone therapy experience and concerns

| | N (%) |
|---|---|
| Have you ever taken growth hormone (GH)? | 144 (66.67%) |
| Do you have concerns about... | |
| GH and increased number of skin moles? | 34 (23.78%) |
| GH and excess hair growth? | 28 (19.44%) |
| GH and swelling? | 34 (23.78%) |

**Quality-of-life (QOL) impact**

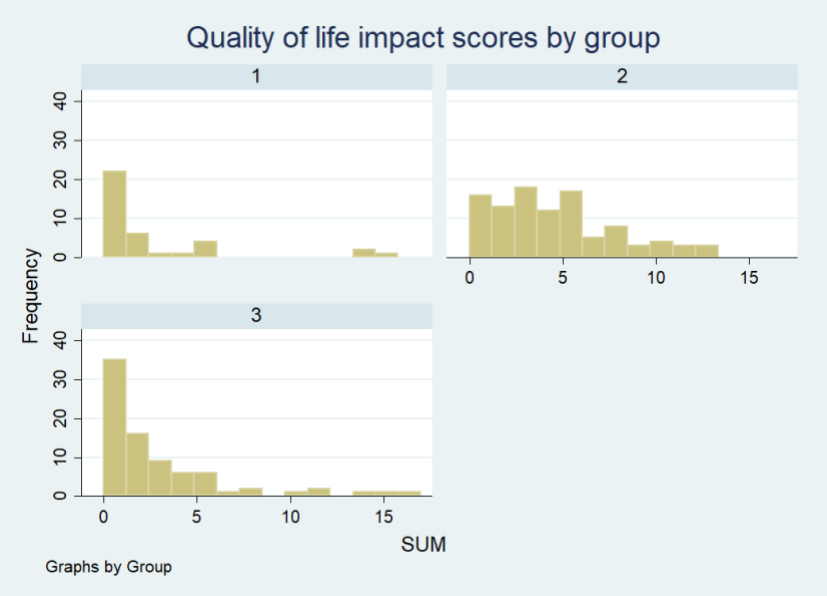
Overall, the mean QOL life impact score was 3.52 (*SD*, 3.42) which corresponds to a small effect on patient lives according to the Dermatology Life Quality Index (DLQI) scoring system. An exploratory analysis with 2x2 contingency tables with measures of association demonstrated that vitiligo with Fischer's exact (95% CI, OR = 21.26, p=0.03), and dry skin, $X^2$ (1, N=220) = 61.59, OR = 60.84, 95% CI, p=0.00) each were associated with a higher QOL impact score. Linear regression confirmed this, with dry skin having the largest relative contribution to quality-of-life impact ($R^2 = 0.92$)

We divided the sample into two groups (High quality of life impact and Low/Average quality of life impact) for further analysis. High QOL impact was defined as those with QOL impact scores two

standard deviations above the mean, which corresponds to scores 11 or higher, reflecting significant impairment to quality of life. 2x2 contingency tables with measures of association showed that abnormal nails ($X^2$ (1, N=219) = 6.33, OR = 6.44, 95% CI, p=0.01), skin biopsy ($X^2$ (1, N=220) = 5.64, OR = 5.47, 95% CI, p=0.02), and lymphedema were all significantly ($X^2$ (1, N=221) = 9.96, OR = 9.25, 95% CI, p=0.00) more prevalent in the group with high QOL scores.

Multivariate test of means showed a significant difference (P<0.05) in the quality-of-life impact scores between samples from the UTH TS registry, TSSUS and Facebook. In particular, the distribution of QOL impact scores was skewed toward higher values when compared to the other two groups (see Figure 1). Given this difference, a separate TSSUS-only exploratory analysis with 2x2 contingency tables with measures of association and t-tests was performed to investigate the validity of our inclusive data analysis. We found that the association between dry skin and higher QOL impact scores persisted in TSSUS. In contrast to the other groups, lymphedema was not significantly associated with QOL. Instead, having more than 20 skin moles was strongly predictive of high QOL impact scores in the TSSUS sample.

Figure 1. Quality of life impact scores by group




*(1) UTHealth research registry (2) Social media groups (3) TSSUS*

## DISCUSSION

This study characterized the prevalence of self-reported dermatological concerns, as well as outline the state of special issues like quality of life impact, treatment-related concerns, treatment utilization, and referral experience to a dermatologist. Our analysis confirmed previous studies and found a high prevalence of dermatological manifestations in a large cohort of Turner syndrome subjects. In addition, our data helps expand on the prevalence of many common skin concerns and recognizes specific age-related times of presentation, presence of family history, and special concerns about dermatological care.

While data outlining the prevalence of skin manifestations has previously not been available, dermatological concerns like lymphedema, hair loss, papules, abnormal nails, >20 skin moles, papules, vitiligo, alopecia, and keloids have been previously outlined as common manifestations associated with TS (Lowenstein et al., 2004, p. 773). Skin cancer was included due to varied data suggesting an unclear relationship between skin moles and cancer Geller et al., 2016, p. 413; Gibbs et al., 2001, p. 1). Dry skin, abnormal scarring, and acne were included as observational trends seen by TS providers.

Dry skin was the most common skin concern with almost 80% of all respondents reporting dry skin starting on average in the second decade of life. This prevalence is significantly higher than the general population and generally starts at an earlier age compared to common age-related skin dryness (Al-Nuaimi et al., 2014). With that, approximately 65% of those with dry skin have a first degree relative with the same concern. This observation is not unexpected, as dry skin is exceedingly common in the general population, regardless of having Turner syndrome (Augustin et al., 2018, p. 148).

One-third of respondents reported a personal history of lymphedema, which is significantly lower than the previously suggested two-thirds frequency at any point across the lifespan. This deviation may be explained by the fact that lymphedema is most common at the time of birth, with 76-95% of infants with TS displaying dorsal swelling. Of those cases, about 37% will resolve by early childhood (Rothbaur & Callender, 2015, p. 148). Given that our study relies on self-report recollection of lymphedema, some respondents may not recall their experience with this concern. This may be due to respondent's

experiencing mild cases of lymphedema in early infancy that soon resolved. Our analysis supports this assertion in that independent adult responders reported a history of lymphedema at a rate of 27.93%, while parent responders reported lymphedema in their child with TS at a rate of 55%. Still, the average self-reported decade of onset was the first decade of life, suggesting that many respondents were aware of their early lymphedema. In terms of treatment experience, our data is consistent with other reports that suggest lymphedema is highly undertreated in the TS population. Although non-invasive treatments like compression garments are widely available, 54.79% of our sample reported no treatment for their lymphedema. Although lymphedema is viewed as a condition that is likely to resolve and not require intervention, it remains a concern that significantly affects quality of life. Statistical analysis showed that a 45,X blood karyotype was predictive of lymphedema.

General hair loss and alopecia were included as separate inquiries due to significant differences between female pattern hair loss and an autoimmune disease like alopecia, which results in patterned baldness. Given that our sample reported significantly more hair loss (37.6%) compared to alopecia (7%), it is likely that the respondents could differentiate between the two concerns. With that, both concerns were first identified in the third decade of life on average. General hair loss had a higher rate of first degree relatives with the same concern. But, it is important to distinguish that general hair loss can be common among the general population, especially at older ages (Birch et al., 2001, p. 299). Treatment for alopecia was reported as much more prevalent than for lymphedema, with 40% receiving corticosteroid injections. Still, over 50% of these individuals reported either no treatment or superficial cosmetic replacements like wigs and makeup.

Abnormal and/or dysplastic nails have been commonly noted as a characteristic feature of TS, often including painful, brittle, convex/concave nails starting in infancy or childhood. Our data supported that approximately 40% of individuals with TS experience dysplastic nails with an average decade of onset in the first decade of life.

High quantities of skin moles (>20) and the presence of papules have been commonly noted across TS literature in conjunction with theories and suggestions about a potential relationship with skin

cancer (Geller et al., 2016, p. 413). A high propensity of skin nevi and/or abnormal papules on the body are objective risk factors for cancers like melanoma and basal cell carcinoma. Some studies have shown an increased risk of skin cancer with TS, while most show that the prevalence is much lower than that of the general population. Our data showed a high prevalence of more than 20 skin nevi (70%) with an average onset in the first decade of life. With that, the positive family history rate was high at 60%, which likely accounts for some of these reports. Papules were commonly noted, with 40% of our sample reporting a positive personal history. Less than 10% of our sample reported a personal history of skin cancer, with an average onset in the fourth decade of life. This prevalence is significantly lower than the general population frequency of 20%, suggesting that women with TS are at lower-than-average risk for skin cancer (Rogers et al., 2015, p. 1081). Significant predictors of skin cancer were an increased number of skin nevi—with approximately 90% of cases reporting >20 skin moles—and the presence of papules. Approximately 38% of our sample had a personal history of skin biopsy due to a suspicion for cancer, where an increased number of skin moles was a significant predictor, as well.

Vitiligo was significantly more prevalent in our sample (6.05%) compared to the general population of 2%, with an average onset in the second decade of life that is consistent with the general average of 20-years-old (Krüger & Schallreuter, 2012, p. 1209). Like lymphedema, vitiligo was highly untreated, with approximately 62% of affected individuals not receiving any treatment. Commonly available treatments like topical medications and light therapy were used approximately 45% of the time, with one respondent using both therapies. Given that success rates for noninvasive treatment options like phototherapy for vitiligo are 51.4% for at least a mild response, proper dermatology referrals and treatment options are imperative (Bae et al., 2017, p. 666).

Keloids have often been reported as a characteristic of TS, especially in high-impact areas that correspond with TS-related surgeries like the neck or chest (Lin et al., 2019, p. 2001). Historically, the recommendation has uniformly been to avoid invasive intervention when possible, even down to small procedures like ear piercings. But, data has suggested that the prevalence of keloids is highly variable and difficult to predict among the TS population. Looking beyond TS, keloids themselves are highly variable

among other defining characteristics like race and/or ethnicity. Those of African American descent and Hispanic/Latinos are at a much higher risk for developing keloids with estimates reaching 16%. Those of Caucasian descent have a much lower propensity for keloids at approximately 0.1% (Sun et al., 2014, p. 805). Given that the majority of our sample was Caucasian, we used 0.1% as a more appropriate general population frequency. With that, our sample showed a personal history of keloids about 40% of the time, often with an onset in the second decade of life. The most common areas of the body to experience keloids were the chest and back. The chest is a high-impact area that may correspond to cardiovascular procedures, and future investigations into the relationship between those with surgeries and keloids should be pursued. Like keloids, some literature and clinical observation has demonstrated a relationship between abnormal and/or hypertrophic scarring and TS. Our sample showed that 28.7% had a personal history of abnormal scarring and/or wound healing. Statistical analysis showed that 45,X and 45,X/46,XX blood karyotypes were predictive of keloids.

Given the impact of abnormal pubertal development with a high proportion of TS girls, acne has often been shown as a less common manifestation compared to the general teenage population. Our sample confirmed that acne is much less common among TS girls. When acne is present, progesterone therapy is present 75% of the time, which may be a predictive factor.

Alongside prevalence data, we aimed to understand the frequency of growth hormone (GH) therapy usage, as well as side effect concerns among the TS population. Our sample reported a rate of two-thirds using GH therapy at some point in their lifespan. Of those, 23.78% had concerns about increased number of skin moles, 19.44% had concerns about excess hair growth, and 23.78% had concerns about swelling. We theorized that some of the concern for skin moles and swelling may be explained by a personal history of related conditions. With that, 5.88% of those with skin mole concerns had a history of skin cancer, and 55.88% with a concern for swelling had lymphedema.

The Dermatology Life Quality Index (DLQI) is a validated 10-point scale used to measure dermatology-specific quality-of-life impact scores. Our sample demonstrated a mean score of 3.52 (*SD* = 3.42), which falls in the predetermined category of “small effect on quality of life”. More in-depth

analysis demonstrated that two skin conditions had a statistically significant negative impact on quality of life; vitiligo and dry skin. Overall, dry skin had the largest relative contribution to this detrimental effect on quality of life. This data suggests that dry skin may be a newly discovered predictor of an underlying mechanism or health condition that is severely affecting the QOL of TS patients. When split into groups by high quality-of-life impact (>10 score) and low/average quality of life impact (<11 score); abnormal nails, skin biopsy, and lymphedema were associated with a high QOL impact. This data suggests that a large proportion of TS-related skin conditions are significantly associated with a high impact on quality of life and require appropriate recognition by providers to mediate this effect.

The literature suggests that the widely-accepted recommendation for TS management is that providing a dermatology referral at the time of diagnosis and continued annual follow-up is an appropriate guideline (Lin et al., 2019, p. 1991). Given that a large proportion of TS-related manifestations like lymphedema, skin moles, and dysplastic nails are present from the first decade of life, specialized dermatology care is crucial for proper TS management from an early age. With that, many other concerns onset soon after, in the second or third decade of life, demonstrating a need for routine care across the lifespan. Our sample reported that 63.95% have been referred to see a dermatologist, with only 33.1% being referred by a TS provider. Further, only a small percentage (9.79%) were referred at the time of diagnosis, even with care guidelines recommending a referral at that time. Approximately 80% of our sample reports that they could self-identify their dermatological concern and bring it up to their provider. Regardless of referral experience, 57.59% of our sample is currently concerned about their skin, and 23.21% want to see a dermatologist. This data suggests that the status of care is falling short of the recommendations to help identify and treat dermatological manifestations that are common among the TS population. Providers that are caring for women and girls with Turner syndrome should consider altering their standards to include dermatology at the time of diagnosis with annual follow-up.

Early diagnosis and intervention has been a consistent concern reported in TS literature due to the later onset hallmark signs and symptoms like gonadal failure not presenting until the second decade of life. Even then, not all women and girls with TS experience noticeable gonadal failure due to mosaicism.

Early signs of TS like lymphedema, high quantities of moles, dry skin, papules, alopecia, vitiligo, and others may not currently aid in earlier diagnosis, as they are often prevalent in the general population or present in first degree relatives. So, clinicians may be inclined to explain TS-related dermatological concerns in an undiagnosed individual due to a positive family history. Our data demonstrates that each TS related concern reported by our respondents has a positive family history rate of at least 35% or more in the individuals with each condition. Thus, our data show that clinicians should utilize these common dermatological manifestations to aid early TS diagnosis even in the presence of a positive family history.

On the basis of our data, comprehensive Turner syndrome care should include a dermatology referral at the time of diagnosis, with routine annual follow-up to address the wide range of conditions that affect physical and emotional wellbeing of patients. Robust strengths of our data include a large, multi-group analysis that included TS patients from a wide range of age groups and karyotype statuses. A clear limitation of this study's methodology includes the self-report nature of our data. Self-report data includes risk for recall bias by respondents regarding their personal experience with the dermatological concerns queried in the survey. Relying on data collected without physical or clinical evidence can affect our conclusions by creating associations that do not truly exist, or omitting relationships that do. Ideally, a study investigating the prevalence of clinically relevant manifestations would include data that can be confirmed with chart review. With that, we targeted cohorts that would likely ensure that a true clinical or genetic TS diagnosis was present in our respondents. Members of research registries, national organizations, and TS-specific social media groups are likely active, knowledgeable participants in their diagnosis and treatment. Additional definitions and explanations of relevant symptoms and conditions were included to enhance understanding and facilitate accurate recall. Lastly, the homogeneity of race and ethnicity (skewed to a Caucasian and Non-Hispanic Latina majority) introduces limitations to the interpretability of our data to these populations, where certain skin conditions may be at higher or lower prevalence based on ethnicity or race alone. Overall, our analysis provides evidence to corroborate a recommendation for routine dermatology care for patients with Turner syndrome in order to address significant physical and emotional impacts.

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