Total body water and sicca symptoms in primary Sjögren's syndrome

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Abstract

Objective

To evaluated the total body water (TBW) among patients with primary Sjögren's syndrome (pSS) and assess its correlation with the severity of oral and ocular sicca symptoms, and some objective sicca variables.

Methods

We included 85 patients and 85 controls matched by sex, age, and body mass index (BMI). We assessed the Schirmer-I test and the non-stimulated whole salivary flow (NSWSF). We evaluated ocular and oral symptoms during the past 15 days using a 0-10 visual analogue scale (VAS) (highest score=worst symptoms). We obtained the TBW by bioelectric impedance analysis.

Results

80% were women (mean age 54.8 years and mean disease duration 11.5 years). TBW was similar in pSS and controls (46.8±4.6 vs. 46.9±4.5, p=0.88). TBW correlated with age (ϱ=-0.25, p=0.02), disease duration (ϱ=-0.30, p=0.005), BMI (ϱ=-0.78, p=0.001) and ocular VAS scale (ϱ=-0.28, p=0.01); but not with NSWSF, Schirmer test or oral VAS scale. When comparing patients in the lowest TBW percentile (≤25%) with the remaining patients, the former group was older, had longer disease duration, higher BMI, lower frequency of anti-Ro/SSA and antinuclear antibodies, and higher ocular VAS scores. In the multivariate analysis, the ocular VAS score (OR 1.88, 95% CI 1.08-3.2, p=0.02) and the BMI 1.92 (OR 1.4, 95% CI 1.4-2.66, p=0.0001) remained associated with a lower TBW percentage.

Conclusion

Patients with pSS had similar TBW percentages to control subjects. However, lower TBW percentages in the pSS were associated with higher BMI and also with the most severe ocular symptoms.

Key words

Sjögren's syndrome, total body water, sicca symptoms, oral symptoms, ocular symptoms

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by immune-mediated damage of exocrine glands, predominantly salivary and lacrimal, with subsequent development of keratoconjunctivitis and xerostomia. Therefore, patients with pSS suffer from severe alterations in the quality and quantity of saliva and tears (1). Although the pathogenesis is still unclear, it is thought to be a multifactorial process involving environmental, genetic, and immunological factors. Recently, it has been suggested that glandular hypofunction may also result from immune mediated inhibition of secretory processes rather than the classical model where glandular tissue is lost through a combination of apoptosis and cytotoxic cell death (2).

For instance, the inability to increase water permeability as part of the stimulus secretion process is a plausible mechanism contributing to glandular hypofunction. In this context, abnormal expression and localisation of aquaporoin-5 (AQP5), a water-permeable channel, has been described in these patients (3).

On the other hand, body water is the main constituent of the human body, and accounts for about 50% of body weight. Total body water (TBW) consists of intracellular and extracellular water, which represent about 2/3 and 1/3, respectively. Intracellular water determines the cellular volume; whereas extracellular water includes interstitial fluid, plasma and other transcellular fluids. TBW is essential for cellular homeostasis and electrolyte balance (4). Tears are composed of 98% of water as well as salts, proteins and mucin; and when blinking, water evaporates from the exposed tear film at the ocular surface (5). Furthermore, saliva is an extracellular fluid containing 99.5% water as well as electrolytes, mucus, enzymes and antimicrobial agents (6).

Determining the body liquid volume has been useful in some diseases such as renal disorders and heart failure (7, 8). Moreover, the ratio between extracellular and intracellular fluid has been proposed as an index of health status (9). Nevertheless, TBW has not been previously evaluated in patients with PSS who suffer from impaired production of tears and saliva, both of them as previously mentioned constituted by a high percentage of water.

Therefore, our aim was first to assess whether the percentage of TBW was similar in patients with PSS and controls. Then, we specifically wanted to assess the intensity of oral and ocular sicca symptoms and some objective sicca variables that might correlate with TBW in PSS patients.

Methods

Study subjects

This is a transversal study that included 85 consecutive patients with pSS who regularly attended to the Rheumatology Department of the Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico, a tertiary referral hospital from February 2019 to January 2020. To be included, all the patients met the ACR/EULAR classification criteria for SS (10). We excluded patients with any other concomitant connective tissue diseases, limb amputation, cardiac pacemaker, insulin pumps, artificial joints, as well as pregnancy or breastfeeding period.

We also included healthy controls (n=85) matched by sex, age (±3 years), and body mass index (BMI) (±1kg/m^2). Patients were asked to refrain from eating, drinking, smoking, chewing, or oral hygiene procedures for at least 1 hour before the evaluation, and were seen in a closed room with no air-conditioning or heating, during the morning. On the day of the evaluation, all PSS patients were subjected to a standardised interview with the same rheumatologist. The Schirmer-I test was done using two standardised sterile tear measurement strips (10). The non-stimulated whole salivary flow (NSWSF) was performed using the spitting method (11). Subjects were instructed to rest for 5 min before the test, minimise orofacial movements, and not to speak. Before starting the procedure, the patient swallowed any residual saliva and then spit it into a graduated test tube every minute. Saliva was collected for a period of 15 min and the measured volume was expressed in ml/15min.

Table I. Clinical and biochemical features among pSS patients.

Variable	n=85
Females, n (%)	80 (94.1)
Age in years, mean ± SD	54.8 ± 13.7
Ocular symptoms, n (%)	78 (91.7)
Oral symptoms, n (%)	79 (92.9)
Parotid gland swelling, n (%)	38 (44.7)
NSWSF in ml/15 min, median (IQR)	0.10 (0.05-0.5)
Impaired NSWSF, n (%)	81 (95)
Median cumulative ESSDAI score, IQR	8 (4.5-14)
Positive Schirmer test, n (%)	76/84 (90.4)
Keratoconjunctivitis sicca, n (%)	44/60 (73.3)
Positive minor salivary gland biopsy, n (%)	59 (69.4)
Antinuclear antibodies, n (%)	66/82 (80.4)
Rheumatoid factor, n (%)	57/81 (70.3)
Anti-Ro/SSA antibody, n (%)	73/84 (86.9)
Anti-La/SSB antibody, n (%)	42/84 (50)
Mean oral VAS score ± SD,	7.1 ± 2.4
Mean ocular VAS score ± SD	7.1 ± 2.4
Body mass index, mean ± SD	25.5 ± 4.8
Fat free mass in kg, mean ± SD	39.3 ± 6.7
Exercise, n (%)	24 (28.2)
Oestrogen current use, n (%)	4 (4.7)
Current use of drugs associated with dryness, n (%)	7 (8.2)

NSWSF: non-stimulated whole salivary flow; VAS: visual analogue score; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

We also retrospectively retrieved the following data on standardised formats from the medical charts: demographics, age at diagnosis, length of follow-up, salivary gland biopsy, the ever presence of keratoconjunctivitis sicca (diagnosed by OSS or Bijsterveld staining score), serology (anti-Ro/SSA, anti-La/SSB antibodies, rheumatoid factor, antinuclear antibodies as well as low C3 and/or C4). We retrospectively scored the cumulative EULAR Sjögren's syndrome disease activity index (ESSDAI) (12).

For the assessment of ocular and oral sicca symptoms, patients were asked to rate individually the severity of each dryness feature (ocular and oral) using a 0–10 VAS scale for each domain using a 15-day recall. A higher score meant the worst symptoms. We also asked about the current use of oral oestrogens and drugs associated with dryness (anticholinergics, antihistamines, antidepressants, diuretics, opioids), and exercise (at least 1 hour per week).

Anthropometric and total body water assessment

All subjects were asked to fast for 10-12 hours, not to exercise in the previous 12 hours, not to drink alcohol, and not to drink coffee the previous day. Metal objects were removed and the study was performed barefoot and in light clothing. We determined TBW percentage by bioelectric impedance analysis (BIA-SECA-514, Hamburgo).

Briefly, the BIA-SECA-514 consists of a platform with an integrated scale and a handrail system. On each side of the raising handrail, there are 6 electrodes, 2 of which are selected according to the height of the person. To obtain the correct grip position, the subject had to stand upright with arms outstretched. Another 2 pairs of electrodes were placed on the feet. This 8-electrode technique enables segmental impedance measurement (13). Then the prediction equations for TBW and fat-free mass were calculated, since this last variable could affect the TBW determination. In addition, we measured weight and height and calculated the BMI.

Statistical analysis

We used descriptive statistics and the U-Mann Whitney test or the student t-test. We used Spearman correlation analysis to evaluate the correlation of TBW with some of the variables. We also performed logistic regression for comparing patients in the ≤25 percentile *vs*. >25 percentile of TBW and reported OR with 95% CI. Two-tailed $p<0.05$ was considered significant. All analyses were performed using SPSS for Windows 20.0.

This study was approved by the Institutional Biomedical Research Board of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

Results

General characteristics

We included 85 patients with pSS and 85 controls. Most of the patients were women (n=80, 94.1%) with a mean age of 54.8±13.7 years and a mean disease duration of 11.5±7.52 years. Table I shows the clinical and serological features of the pSS patients. The mean age of the control group was 54.9±13.5 years, 80 were women, with a mean BMI of 25.9 ±4.5 (p=0.58) and a fat-free mass 44.4±1.85 (p=0.27).

Total body water

The percentage of TBW was similar among patients and controls (pSS 46.85±4.6 *vs*. 46.9±4.5, p=0.88). Among pSS patients, we observed a negative correlation of the TBW with age (ϱ=-0.25, p=0.02), disease duration (ϱ=-0.30, p=0.005), BMI (ϱ=-0.78, p=0.001) and the ocular VAS scale (ϱ=-0.28, p=0.01); but not with the NSWSF, Schirmer-I test or the oral VAS scale.

When we compared patients (n=21) in the ≤25% TBW percentile (the lowest % water *vs*. the remaining patients in higher percentiles (n=64) (Table II), the former group was older (58.6±8.1 *vs*. 54±14.2, p=0.02), with longer disease duration (12.4±5.9 *vs*. 10.8±7.12, p=0.03), higher BMI (31.1±5.1 *vs*. 23.7±2.9, p=0.001), lower frequency of anti-Ro/SSA antibodies (70% *vs*. 92.2%, p=0.01) and ANA (65% *vs*. 85.5%, p=0.04), and higher ocular VAS score (8.3±1.4 *vs*. 6.7±2.5, p=0.007). At the logistic regression analysis adjusted by age, disease duration, anti-Ro/SSA and ANA positivity; the ocular VAS score (OR 1.88, 95% CI 1.08-3.2, p=0.02) and the BMI 1.92 (OR 1.4, 95% CI 1.4-2.66, p=0.0001) remained associated with TBW.

Discussion

Water is the most abundant component of the human body, comprising 45%-75% of body weight. Intracellular and extracellular fluid concentrations are

Table II. Comparison of patients according to ≤25 percentile *vs*. >25 percentile of TBW status.

Variable	Percentile ≤25 TBW n=21	Percentile> 25 TBW n=64	*p*-value
Female, n (%)	20 (95.2)	60 (93.8)	0.80
Age, years ± SD	58.6 ± 8.1	54 ± 14.2	0.02
Disease duration in years, means ± SD	12.4 ± 5.9	10.8 ± 7.12	0.03
Ocular symptoms, n (%)	21 (100)	57 (89.1)	0.14
Oral symptoms, n (%)	19 (90.2)	60 (93.8)	0.67
Parotid gland swelling, n (%)	11 (52.4)	27 (42.2)	0.41
Median cumulative ESSDAI score[§], IQR	9 (6-14.5)	7.5 (4-13)	0.23
NSWSF in ml/15min, median (IQR)	0.1 (0-0.4)	0.1 (0.1-0.5)	0.85
Impaired NSWSF, n (%)	19 (90.4)	62 (96.8)	0.25
Keratoconjunctivitis sicca, n (%)	12/17 (70.6)	32/43 (74.4)	0.76
Positive Schirmer test, n (%)	20 (95.2)	56/63 (88.8)	0.39
Antinuclear antibodies, n (%)	13 (65)	53 (85.5)	0.04
Rheumatoid factor, n (%)	15 (75)	42 (68.9)	0.60
Anti-Ro/SSA antibody, n (%)	14 (70)	59 (92.2)	0.01
Anti-La/SSB antibody, n (%)	9 (42.9)	33 (51.5)	0.48
Mean oral VAS score ±SD[‡],	7.6 ± 2.2	7.0 ± 2.4	0.96
Mean ocular VAS score ± SD,	8.3 ± 1.4	6.7 ± 2.5	0.007
Body mass index, mean ± SD	31.18 ± 5.1	23.7 ± 2-9	0.0001
Fat free mass in kg, mean ± SD	40.3 ± 8.2	39.0 ± 6.2	0.44
Exercise, n (%)	3 (14.2)	21 (32)	0.10
Oestrogen current use, n (%)	2/20 (10)	2/60 (3.3)	0.23
Current use of drugs associated with dryness	3 (14.2)	4 (6.2)	0.09

TBW: total body water; NSWSF: non stimulated whole salivary flow; VAS: visual analogue score; ESSDAI: EULAR Sjögren's syndrome disease activity index.

regulated by plasma osmolality and a complex, dynamic network of sensory nerves, autonomic neuroendocrine responses, and central brain integration (4, 14). Several techniques for the assessment of hydration status have been employed including deuterium dilution, biochemical markers (atrial and brain natriuretic peptide levels, 24 h urine osmolality, urine colour, and volume) (15), ultrasonography parameters (inferior vena cava diameter and continuous blood volume measurements), and catheterisation (16). Furthermore, bioelectrical impedance analysis (BIA) is a simple, rapid, non-invasive, and reliable technique for the *in vivo* measurement of TBW (8, 13, 15).

The extracellular water/TBW ratio is a useful indicator for assessing nutritional status and fluid status (9). For example, under-hydration has been associated with chronic kidney disease, diabetes, urinary tract infection, and reduced cognitive performance (7, 8, 16). Conversely, an increase in TBW was linked with adverse outcomes in patients on haemodialysis and heart failure (7, 8).

pSS is a disease with impaired production of tears and saliva, both of them constituted by a high percentage of water. It is also known that altered distribution and localisation of AQP5 is associated with impaired secretory function. AQP5 mediates fluid transport from the corneal stroma into the tears and contributes to maintaining tear film isotonicity. Also, proper translocation of AQP5 to the apical plasma membrane of salivary acinar cells is essential for hypotonic saliva production (3).

No previous study has investigated whether TBW contributes to the intensity of sicca symptoms in pSS. In addition, because an inconsistent correlation between subjective and objective measures has been previously described in the assessment of xerophthalmia and xerostomia (stronger for ocular symptoms) (17), we also included at least one objective ocular and oral sicca test to assess their association with TBW. Herein, we observed no differences in TBW among the pSS and controls. TBW in our patients was 46.8%; in agreement, a former study that also assessed the body composition with bioelectrical impedance in pSS patients reported a similar figure (47.2%) (18).

TBW has been described to decrease with age and to vary with sex. Moreover, it becomes progressively lower with increasing obesity or with loss of muscle mass (4). These factors also apply for SS patients, for instance, in the present study, we found a negative correlation between age and BMI in our patients.

We also observed that the patients with the lowest TBW values had the highest intensity of ocular sicca symptoms; a finding that was independent of disease duration, age, anti-Ro/SSA or ANA positivity and BMI. In contrast, we did not find an association with the Schrimer I test and TBW. Active and passive water and solute transport through the conjunctiva also has an important interplay with tear osmolarity. Indeed, tear hyperosmolarity is the main inflammatory mechanism in both aqueous-deficient (including pSS patients) and evaporative dry eye; and is determined by the interaction of tear production, evaporation, and drainage (19-20). Also, the measurement of basal tear osmolarity has been proposed as a screening test for preclinical and clinical dehydration (21).

On the other hand, we found no association between TBW and the intensity of oral symptoms or the NSWSF. Total water intake has been positively correlated with TBW (22) and is determined by intake (beverages, food, and metabolic water) and waste (urine, stool, skin, exhaled air from lungs). Paradoxically, Nesvold *et al*. reported that pSS patients with higher subjective oral dryness and worst oral health-related quality of life had a higher intake of beverages evaluated by a 24-h recall questionnaire (18), possibly as a compensatory mechanism.

Finally, we evaluated other variables that might be associated with TBW. For instance, both oestradiol and progesterone can influence the complex neural and hormonal system evolved in the control of thirst and fluid intake (23). In our study, we did not find any association with the use of oral oestrogens and TBW, nor with the performance of exercise. Moreover, at the univariate analysis, patients with the lowest TBW percentile were more often seronegative for anti-Ro/SSA and ANA antibodies, a serologic phenotype that has been associated with a high burden

of sicca symptoms in some studies. For example, Chatizis *et al*. observed that triple seronegative (anti-Ro/SSA, anti-La/SSB, RF and ANA) patients were more likely to have dry mouth, whereas patients who were quadruple seronegative [anti-Ro/SSA, anti-La/SSB, RF and ANA] were more likely to have dry eyes (24). Conversely, in the Sjögren's Big Data cohort, ANA positivity was associated with a higher frequency of abnormal ocular tests but a similar frequency of dry eye and mouth symptoms. In addition, anti-Ro+ patients had a lower frequency of dry mouth and eyes, whereas anti-La+ patients had a higher frequency of ocular and oral symptoms (25).

Our study has the following limitations. First, TBW was not obtained by deuterium dilution, which is the reference method for measurement. Nevertheless, the agreement between bioimpedance and isotope dilution techniques has been reported (6-9). Second, we did not evaluate tear osmolarity and other ophthalmological tests besides Schirmer-I test. We also did not assess stimulated salivary flow that has been proposed by some authors as a more reliable way of evaluating glandular function (26). A previous study in pSS described a lower proportion of impaired stimulated salivary flow than NSWSF (61.8% *vs*. 82.4%, respectively) (27); thus, we do not know if TBW might have an impact in this outcome. Nevertheless, NSWSF is also considered to be a valid method for the evaluation of salivary function. Finally, we did not evaluate the interrelationship of dietary water intake, activity level, and environmental factors (season and climate) that might also impact the TBW.

Summing up, patients with pSS had similar TBW percentages to control subjects. However, lower TBW percentages in the pSS group were associated with higher BMI and also with the most severe ocular symptoms.

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