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"TO EVALUATE SALIVARY GLAND FUNCTION USING SCINTIGRAPHY IN INDIVIDUALS DIAGNOSED WITH SJÖGREN'S SYNDROME AND TO CONTRAST THE RESULTS WITH THOSE OF CONTROL SUBJECTS."

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ABSTRACT **Introduction:** Sjögren's syndrome (SS) is an autoimmune disease affecting the salivary and lacrimal glands leading to xerostomia – dryness of mouth and keratoconjunctivitis sicca – dryness of eyes. Primary Sjögren's syndrome (PSS) is one of the common autoimmune diseases, with a prevalence rate ranging from 0.1% to 4.6%.[1] The prevalence of secondary Sjögren's syndrome (SSS) associated with rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis has been estimated to be 17.1%,[4] 8% to 20%,[2,3,4] and 14%,[5] respectively. Dysregulation of T cells and B cells is central to the pathogenesis of PSS with innate pathways of inflammation also being involved. Imaging modalities include sialography, salivary scintigraphy, ultrasonography of salivary glands, computed tomography and MR Sialography. **Aim And Objectives:** To assess salivary gland function by scintigraphy in patients with Sjögren's syndrome and to compare with controls. **Material And Methods:** This was a cross-sectional analytical study conducted in the Department of Nuclear Medicine at Jawaharlal Institute of Postgraduate Medical Education and Research, India with Study duration *of* 2 years *i.e* from September 2013 to August 2015. The cases referred from Department of Clinical Immunology after satisfying the necessary inclusion and exclusion criteria. Patients who were either suspected/confirmed Primary Sjogren syndrome or suspected/confirmed Secondary Sjogren Syndrome was referred to the department for the evaluation of function parotid and submandibular salivary glands using Dynamic Salivary Gland scintigraphy were enrolled in the study after obtaining proper informed consent. Patients scheduled for salivary scintigraphy have been assessed for presence and grade of xerostomia based on a questionnaire comprising of 8 questions (XQ Questionnaire-University of Michigan).[6] Xerostomia score of 0 to 10 has been recorded as per the patient's response to the questionnaire. After intravenous administration of approximately 370 Mega Becquerel (MBq) [10 millicuries (mCi)] ^{99m}Tc-sodium pertechnetate, dynamic images of 60 second per frame were acquired in anterior projection with head and neck in the field of view, for 30 minutes on a dual head gamma camera (Siemens Symbia SPECT-CT T6 series) using a low energy, high resolution, parallel hole collimator. The images have been digitally recorded in a 128 x 128 matrix with a 140-kilo electron volts (Kev) photopeak for ^{99m}Tc. At 15 minutes through the dynamic acquisition, the patient has been administered freshly squeezed 2 ml of lemon juice orally, and imaging was continued for further 15 minutes. Later quantitative assessment of salivary gland function has been done. The healthy controls referred for evaluation of the thyroid gland function for disorders such as nodular goiter from Dept of ENT included after satisfying the necessary inclusion and exclusion criteria referred done same as cases. The estimated sample size was 60 each for cases and controls. **Results:** The mean age (SD) in cases was 42.34 (11.64) years and was comparable with healthy controls 40.97 (12.79) years with no statistically significant difference $p = 0.996$. In both cases and controls females constituted 88 % of the participants and males constituted the rest 12%. There was no significant statistical difference in gender distribution between the cases and controls; $p = 0.428$. The SGS quantitative parameters of parotid glands such as EF % and SV % have statiscally significant difference between cases and controls ($p < 0.001$ and $p = 0.001$ respectively). Quantitative parameter MA_{15} % of parotid did not show any statistical significant difference between cases and controls ($p = 0.285$). The SGS quantitative parameters of submandibular glands namely EF %, SV % and MA_{15} % have shown statistical significant difference between cases and controls ($p = 0.008$, $p = 0.012$ and $p = 0.034$ respectively). On comparison of quantitative parameters between and within groups of PSS, SSS and healthy controls there was statistically significant difference was seen in EF % and SV % of parotid glands ($p < 0.001$ and $p < 0.001$ respectively) and EF % and SV % of submandibular glands ($p = 0.02$ and $p = 0.024$ respectively) The quantitative parameters MA_{15} % in both parotids ($p = 0.187$) and submandibular glands ($p = 0.779$) did not show any statistical significant difference between PSS, SSS and healthy controls. In the study, the correlation between the xerostomia score and SGS quantitative parameters in cases was not statistically significant ($p > 0.05$) or correlative ($r < 0.7$) (either positive or negative). There was no statistically significance ($p > 0.05$) or correlative (either positive or negative) ($r < 0.7$) between SGS quantitative parameters and xerostomia score in patients with PSS and SSS. There was statistically significant positive correlation between EF % and SV % of parotid glands ($r = 0.872$) and between EF % and SV % of submandibular glands ($r = 0.841$) in cases. However, there was statistically significant positive correlation between EF % and SV % of parotid glands ($r = 0.872$) and between EF % and SV % of submandibular glands ($r = 0.841$) in cases. Statistically, a significant positive correlation was found between EF % and SV % of parotid glands ($r = 0.893$) and between EF % and SV % of submandibular glands ($r = 0.921$) in PSS. Similarly, a statistically significant positive correlation was observed between EF % and SV % of parotid glands ($r = 0.863$) and between EF % and SV % of submandibular glands ($r = 0.816$) in SSS. The correlation was higher in PSS patients than SSS patients. **Conclusion:** Quantitative parameters such as Excretion-Fraction % and Secretion-Velocity % in parotid glands and Excretion-Fraction %, Secretion-Velocity % and Maximum-$Accumulation_{15}$% in submandibular glands were statistically significant between the two groups. However, there was no statistically significant correlation between xerostomia-score derived from Xerostomia-Questionnaire and quantitative parameters derived from salivary scintigraphy in cases. Therefore, it can be said that the quantitative parameters (EF %, SV %) in parotid glands (EF %, SV % and MA_{15} %) in submandibular glands may be considered to be sensitive parameters in the assessment of salivary gland function in cases of primary and secondary Sjögren's syndrome. Also, further studies have to be done to validate xerostomia questionnaire in patients affected with Sjögren's syndrome and to correlate with quantitative parameters of salivary scintigraphy.

KEYWORDS : Primary Sjögren's syndrome (PSS) , Secondary Sjögren's syndrome (SSS) , Dynamic Salivary Gland scintigraphy (SGS) , Xerostomia.

INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune disease affecting the salivary and lacrimal glands leading to xerostomia – dryness of mouth and keratoconjunctivitis sicca – dryness of eyes. Primary Sjögren's syndrome (PSS) is one of the common autoimmune diseases, with a prevalence rate ranging from 0.1% to 4.6%.[1] The incidence and prevalence rates of primary SS are significantly higher in females than males (e.g., approximately 20: 1), with a peak incidence in the 5th and 6th decades of life.[2] In a study conducted by R Misra et.al. at a specialized rheumatology clinic in North India the percentage patients with Primary Sjögren's syndrome were 0.5 % over a period of ten years. The prevalence of secondary Sjögren's syndrome (SSS) associated with rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis has been estimated to be 17.1%,8% to 20%,[2,3,4] and 14%,[5] respectively. Dysregulation of T cells and B cells is central to the pathogenesis of PSS with innate pathways of inflammation also being involved. There is a loss of immunological tolerance to self-antigens which is seen in any autoimmune disease. There is a loss of B cells self-tolerance leading to the production of serum autoantibodies and loss of T cells self-tolerance leading to infiltration of the lacrimal and salivary glands of patients.[8] Imaging modalities include sialography, salivary scintigraphy, ultrasonography of salivary glands, computed tomography and MR Sialography. Salivary gland scintigraphy (SGS) is a simple, non-invasive procedure that can quantify the function of major salivary glands such as parotids and submandibular in one single study. Assessment of salivary gland function by salivary scintigraphy can be assessed both qualitatively by visual analysis and by quantitative or semi-quantitative analysis. Various quantitative parameters for example such as computer-assisted time–activity curves, the percent uptake of counts injected, gland-to-background ratio, uptake slope, time elapsed to peak counts, maximum-to initial count ratio, and gland to thyroid count, Excretion-Fraction(EF), Maximum-Accumulation (MA), Secretion-Velocity (SV) have been derived and validated. Grading system systems have been devised for quantification of salivary gland function by SGS. One such grading based on the visual qualitative analysis is Schall's four category grading system that varies from normal to very severe dysfunction.[9] SGS has an overall sensitivity for Sjogren syndrome of 71–87%, and a specificity of 78.9%.[10,11] SGS has advantage over other studies that it can functionally evaluate all the major salivary glands in one single study, correlates well with histopathologic findings, can provide either quantitative or semi-quantitative analysis and can be used to assess response to treatment. Disadvantage being it cannot depict morphological changes clearly and findings are not specific for SS.

AIMS AND OBJECTIVES

Aim

To assess salivary gland function by scintigraphy in patients with Sjögren's syndrome and to compare with controls.

Objectives

1. To compare and assess excretion fraction, secretion velocity and maximum accumulation in patients with SS (cases) and controls.
2. To compare the differential function of bilateral parotid and submandibular salivary glands in patients with SS and controls.
3. To correlate the level of clinical xerostomia among the patients with SS with SGS findings.

MATERIAL AND METHODS

This was a cross-sectional analytical study conducted in the Department of Nuclear Medicine at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India with Study duration of 2 years i.e from September 2013 to August 2015. The cases referred from Department of Clinical Immunology after satisfying the necessary inclusion and exclusion criteria. Patients who were either suspected/confirmed Primary Sjogren syndrome or suspected/confirmed Secondary Sjogren Syndrome was referred to the department for the evaluation of function parotid and submandibular salivary glands using Dynamic Salivary Gland scintigraphy were enrolled in the study after obtaining proper informed consent.

The healthy controls referred for evaluation of the thyroid gland function for disorders such as nodular goiter from Dept of ENT included after satisfying the necessary inclusion and exclusion criteria referred.

Sample Size: The estimated sample size was 60 each for cases and controls.

Study Procedure

For Cases

Patients scheduled for salivary scintigraphy have been assessed for presence and grade of xerostomia based on a questionnaire comprising of 8 questions (XQ Questionnaire-University of Michigan).[6] Xerostomia score of 0 to 10 has been recorded as per the patient's response to the questionnaire. After intravenous administration of approximately 370 Mega Becquerel (MBq) [10 millicuries (mCi)] ^{99m}Tc-sodium pertechnetate, dynamic images of 60 second per frame were acquired in anterior projection with head and neck in the field of view, for 30 minutes on a dual head gamma camera (Siemens Symbia SPECT-CT T6 series) using a low energy, high resolution, parallel hole collimator. The images have been digitally recorded in a 128 x 128 matrix with a 140-kilo electron volts (Kev) photopeak for ^{99m}Tc. At 15 minutes through the dynamic acquisition, the patient has been administered freshly squeezed 2 ml of lemon juice orally, and imaging was continued for further 15 minutes. Later quantitative assessment of salivary gland function has been done.

For Healthy Controls

Patients scheduled for thyroid cum salivary scintigraphy assessment done in the same way.

CLINICAL ASSESSMENT OF XEROSTOMIA BY XEROSTOMIA QUESTIONNAIRE

Clinical assessment of Xerostomia in both cases and controls has been done with xerostomia questionnaire provided below.

The xerostomia questionnaire (XQ) -University of Michigan.[6]

1. Rate your difficulty in talking due to dryness
2. Rate your difficulty in chewing due to dryness
3. Rate your difficulty in swallowing solid food due to dryness
4. Rate the frequency of your sleeping problems due to dryness
5. Rate your mouth or throat dryness when eating food
6. Rate your mouth or throat dryness while not eating
7. Rate the frequency of sipping liquids to aid swallowing food
8. Rate the frequency of sipping liquids for oral comfort when not eating.

Patients rate each item on a scale from 0 to 10.
A higher score denotes worse xerostomia.

Figure 1- Xerostomia Questionaire

Estimation of Quantitative Parameters

Regions of interest were drawn on each gland and time-activity curves (TAC) were generated from each gland. Quantitative parameters such as Excretion fraction (EF%), Secretion velocity/min (SV%) at 15th minute post sialagogue administration and Maximum accumulation (MA_{15}%) at 15th minute just prior to sialagogue administration were calculated from the time-activity curves. Diagrammatic representation of the above data is shown in the figures below.

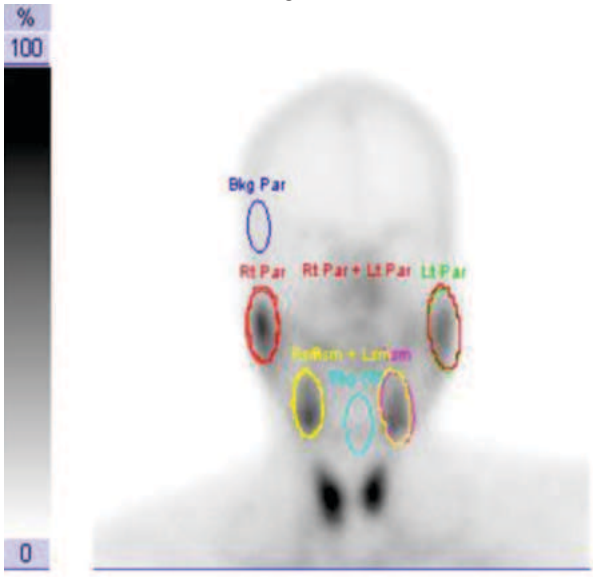


Figure 2- Regions Of Interest Around Each Gland

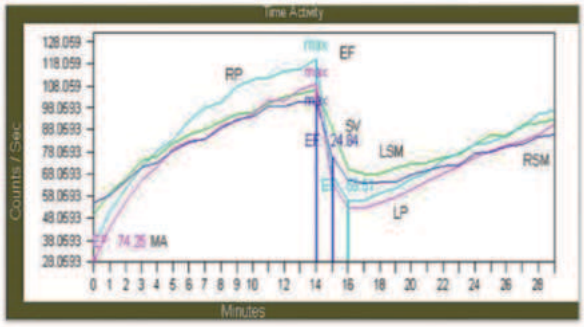


Figure 3 - Estimation Of Various Quantitative Parameters From Time-activity Curves

KEY

EF - EXCRETION FRACTION

SV - SECRETION VELOCITY

MA - MAXIMUM ACCUMULATION AT 15TH MINUTE

RP- RIGHT PAROTID GLAND

LP – LEFT PAROTID GLAND

RSM – RIGHT SUBMANDIBULAR GLAND

LSM – LEFT SUBMANDIBULAR GLAND

MAX- MAXIMUM COUNTS

Figure 4- Key

DEFINITION OF THE QUANTITATIVE PARAMETERS USED

EXCRETION FRACTION (EF %) =

$$\frac{\text{Maximum counts pre-stimulation - Minimum counts post stimulation X 100}}{\text{Maximum counts pre-stimulation}}$$

SECRETION VELOCITY (SV%/min) =

$$\frac{\text{Maximum counts at 15}^{th}\text{ minute -Minimum activity at 16}^{th}\text{ minute X 100}}{\text{Maximum counts at 15}^{th}\text{ minute}}$$

MAXIMUM ACCUMULATION (MA$_{15}$%) AT 15TH MINUTE=

$$\frac{\text{Maximum counts at 15}^{th}\text{ minute -Minimum activity at 1}^{st}\text{minute X 100}}{\text{Maximum counts at 15}^{th}\text{ minute}}$$

Figure 5:quantitative Parameters

The quantification parameters were evaluated per gland basis – each gland is identified as a separate entity and evaluation has been done.

For the patient population of 167 patients - 334 parotid and 334 submandibular glands have been evaluated and time activity curves have been generated.

To compare with the cases equally without any bias, evaluation of salivary gland function has also been done per gland basis. For the healthy control group of 75 participants - 150 parotid and 150 submandibular glands have been evaluated and subsequently time activity curves have been generated.

Data Entry and Analysis

Data entry and analysis was done using SPSS software. Comparison between age and gender distribution between the cases and controls was done using Chi-square test. The data related to quantitative parameters of salivary gland function, and level of xerostomia was expressed as mean with standard deviation. Comparison between quantitative parameters between cases and controls was done using student's t-test. Comparison of quantitative parameters between Primary Sjogren syndrome, Secondary Sjogren syndrome and healthy control groups was done using ANOVA test (Analysis of Variance). Correlation between quantitative parameters and xerostomia score was done using Pearson correlation and depicted by scatter plot matrix.

RESULTS

Table 1- Socio Demographics And Disease Status Of The Study Participants:

SOCIO DEMOGRAPHIC FACTORS	
AGE GROUPS (YRS)	**FREQUENCIES (%)**
18-30	44 (18.2%)
31-45	105 (43.4%)
46-60	76 (31.4%)
61 AND ABOVE	17 (7.0%)
GENDER	
MALES	29 (12%)
FEMALES	213 (88%)
DISEASE STATUS	
PRIMARY SJÖGREN'S SYNDROME	29 (12%)
SECONDARY SJÖGREN'S SYNDROME	138 (57%)
HEALTHY CONTROLS	75 (31%)

Table 2- Comparison Of Socio Demographic Characteristics Between Patients With Sjögren's Syndrome And Healthy Controls:

CHARACTERISTICS	CASES, N (%)	CONTROLS N (%)	p-value
AGE IN YEARS (MEAN±SD)	42.34 ± 11.64	40.97 ± 12.79	
AGE GROUPS (YRS)			
18-30	26 (15.6 %)	18 (24 %)	
31-45	75 (44.9 %)	30 (40 %)	0.996
46-60	53 (31.7 %)	23 (30.7 %)	
61 AND ABOVE	13 (7.8 %)	4 (5.3 %)	
GENDER			
MALE	20 (12 %)	9 (12 %)	0.428
FEMALE	147 (88 %)	66 (88 %)	

Duration Of Xerostomia

The mean duration of xerostomia among the patient group was 15.54 months. The range of duration of xerostomia was from a minimum of zero (i.e.no symptoms of xerostomia even for one month) to 240 months (none to 20 years).

In the PSS group the mean duration of xerostomia was 26.14 months. The range of duration of xerostomia was from minimum of zero (i.e.no symptoms of xerostomia even for one month) to 180 months (none to 15 years).

In the SSS group the mean duration of xerostomia was 13.15 months. The range of duration of xerostomia was from a minimum of zero (i.e.no symptoms of xerostomia even for one month) to 240 months (none to 20 years).

Xerostomia Score

The mean ± SD xerostomia score among the patient group was 17.30 ± 18.67. The range of xerostomia score was from a minimum of 0 (zero) to a maximum of 76.

In the PSS group, the mean ± SD xerostomia score among the patient group was 25.90 ± 21.89. The range of xerostomia score was from a minimum of 0 (zero) to a maximum of 76. In the SSS group, the mean ± SD xerostomia score among the patient group was 15.25 ± 17.42. The range of xerostomia score was from a minimum of 0 (zero) to a maximum of 67.

Table 3- Comparison Of Quantitative Parameters Between Cases And Controls

	CASES	CONTROLS	p VALUE
	MEAN ± S.D.	MEAN ± S.D.	
EF PAROTID (%)	47.16±14.05	52.99±9.87	<0.001
SV PAROTID (%/min)	36.75 ±13.79	41.71 ±10.4	0.001
MA_{15} PAROTID (%)	68.69 ±11.45	67.03 ±11.76	0.285
EF SUBMANDIBULAR (%)	33.60 ±13.21	36.34 ±11.01	0.008
SV SUBMANDIBULAR (%/min)	23.44 ±12.39	25.91 ±10.23	0.012
MA_{15} SUBMANDIBULAR (%)	45.85 ±13.88	45.00 ±15.63	0.034

In the patient group, the mean Excretion-Fraction (EF %) of parotid glands was 47.16% with a standard deviation of 14.05%. The mean Secretion-Velocity (SV %/min) of parotid glands was 36.75% with a standard deviation of 13.79%. The mean Maximum-Accumulation (MA_{15} %) in parotid glands at the fifteenth minute was 68.69% with a standard deviation of 11.45%. The mean EF % of submandibular glands was 33.60% with a standard deviation of 13.21 %. The mean SV %/min of submandibular glands was 23.44 % with a standard deviation of 12.39 %. The mean MA_{15} % in submandibular glands at the fifteenth minute was 45.85 % with a standard deviation of 13.88%.

In the healthy controls, the mean EF % of parotid glands was 52.99% with a standard deviation of 9.87%. The mean SV %/min of parotid glands was 41.71 % with a standard deviation of 10.4%. The mean MA_{15} % in parotid glands at the fifteenth minute was 67.03 % with a standard deviation of 11.76%. The mean EF % of submandibular glands was 36.34% with a standard deviation of 10.23%. The mean SV %/min of submandibular glands was 25.91 % with a standard deviation of 10.23%. The mean MA_{15} % in submandibular glands at the fifteenth minute was 45.00% with a standard deviation of 15.63%.

The quantitative parameter of EF % of parotid glands was statistically significant between cases and controls, $p < 0.001$.The quantitative parameter of SV % of parotid gland was also statistically significant between cases and controls, $p = 0.001$. The quantitative parameter of MA_{15} at the fifteenth minute of the parotid glands did not show any statistically significant difference between cases and controls $p = 0.285$. The quantitative parameters of EF %, SV % and MA % at the fifteenth minute were statistically significant between both the groups, $p = 0.008$; $p = 0.012$ and $p = 0.034$ respectively.

Tests for comparison of means between the two groups was done using Student's t-test.

Table4- Comparison Between Primary Sjögren's Syndrome, Secondary Sjögren's Syndrome Groups With Healthy Controls (Between And Within Groups Comparison)

	CASES		CONTROLS	p VALUE
QUANTITATIVE PARAMETERS	PSS	SSS	MEAN ± S.D.	
EF PAROTID (%)	44.89±17.76	47.63±13.13	52.99±9.87	<0.001
SV PAROTID (%/min)	34.33±16.86	37.25±13.03	41.71 ±10.4	<0.001
MA_{15} PAROTID (%)	67.94±14.88	68.84±10.62	67.03 ±11.76	0.187
EF SUBMANDIBULAR (%)	31.06±16.49	34.13±12.4	36.34 ±11.01	0.02
SV SUBMANDIBULAR (%/min)	21.05±13.58	23.93±12.1	25.91 ±10.23	0.024
MA_{15} SUBMANDIBULAR (%)	46.5±15.59	45.71±13.52	45.00 ±15.63	0.779

In the PSS patients, the mean EF% of parotid glands was 44.89% with a standard deviation of 17.76%. The mean (SV %/min of parotid glands was 34.33% with a standard deviation of 16.86%. The mean MA_{15} % in parotid glands at the fifteenth minute was 67.94% with a standard deviation of 14.88%. The mean EF % of submandibular glands was 31.06% with a standard deviation of 16.49%. The mean SV %/min of submandibular glands was 21.05% with a standard deviation of 13.58%. The mean MA_{15} % in submandibular glands at the fifteenth minute was 46.5% with a standard deviation of 15.59%.

In the SSS patients, the mean EF % of parotid glands was 47.63% with a standard deviation of 13.13%. The mean SV %/min of parotid glands was 37.25% with a standard deviation of 13.03%. The mean MA_{15} % in parotid glands at the fifteenth minute was 68.84% with a standard deviation of 10.62 %. The mean EF % of submandibular glands was 34.13% with a standard deviation of 12.4%. The mean SV %/min of submandibular glands was 23.93% with a standard deviation of 12.1%. The mean MA_{15} % in submandibular glands at the fifteenth minute was 45.71% with a standard deviation of 13.52%.

In the healthy controls, the mean EF % of parotid glands was 52.99% with a standard deviation of 9.87%. The mean SV %/min of parotid glands was 41.71% with a standard deviation of 10.4%. The mean MA_{15} % in parotid glands at the fifteenth minute was 67.03% with a standard deviation of 11.76%. The mean EF % of submandibular glands was 36.34% with a standard deviation of 10.23%. The mean SV %/min of submandibular glands was 25.91% with a standard deviation of 10.23%. The mean MA_{15}% in submandibular glands at the fifteenth minute was 45.00% with a standard deviation of 15.63%.

Quantitative parameters of parotid glands such as EF %and SV %/min was statistically significant between and within the three groups, $p < 0.001$ and $p < 0.001$ respectively. The quantitative parameter of MA15 % at the fifteenth minute of the parotid glands did not show any statistical significant difference between and within the three groups, $p = 0.187$. The quantitative parameters of EF % and SV % statistically significant between and within the three groups, $p = 0.02$ and $p = 0.024$ respectively. The quantitative parameter of MA_{15} % at the fifteenth minute of the submandibular glands did not show any statistical significant difference between and within the three groups, $p = 0.779$.

Tests for comparison of means between and within the three groups was done using ANOVA (Analysis of variance) and post hoc analysis was performed with Scheffe's method.

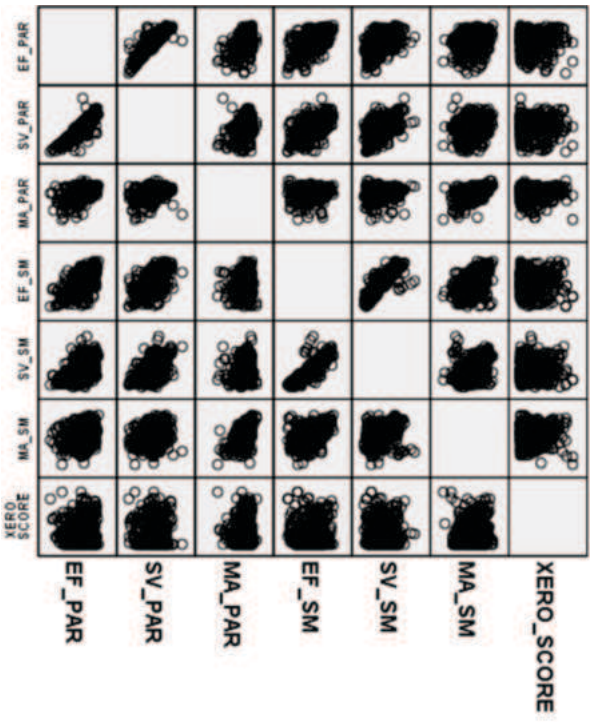


Figure 6- Scatter Plot Depicting Correlation Of Quantitative Parameters And Xerostomia Scores In Patients With Sjögren's Syndrome (ss) (cases).

Table 5-scatter Plot Depicting Correlation Of Quantitative Parameters And Xerostomia Scores In Patients With Sjögren's Syndrome (ss) (cases).

	Excretion fraction in parotid	Secretion velocity in parotid	Maximum accumulation in parotid	Excretion fraction in submandibular	Secretion velocity in submandibular	Maximum accumulation in submandibular	Xerostomia Score
Excretion fraction in parotid		0.872**	0.509**	0.574**	0.476**	0.287**	-0.021
Secretion velocity in parotid	0.872**		0.387**	0.520**	0.533**	0.230**	-0.059
Maximum accumulation in parotid	0.509**	0.387**		0.187**	0.169**	0.556**	-0.024
Excretion fraction in submandibular	0.574**	0.520**	0.187**		0.841**	0.429**	-0.018
Secretion velocity in submandibular	0.476**	0.533**	0.169**	0.841**		0.288**	-0.127
Maximum accumulation in submandibular	0.287**	0.230**	0.556**	0.429**	0.288**		-0.036
Xerostomia score	-0.021	-0.059	-0.024	-0.018	-0.127	-0.036	

** - Correlation is significant at the 0.01 level (2-tailed).
* - Correlation is significant at the 0.05 level (2-tailed).

A correlation was performed between quantitative parameters of parotid and submandibular glands & xerostomia score using Pearson correlation. There was no statistically significant correlation between quantitative parameters and the xerostomia score although xerostomia score had a negative correlation between all the quantitative parameters of both parotid and submandibular salivary glands. However, there was statistically significant positive correlation (r = 0.872) between EF % of parotid and SV % of parotid glands. Also, there was there was statistically significant positive correlation (r = 0.841) between EF % of parotid and SV % of submandibular glands.

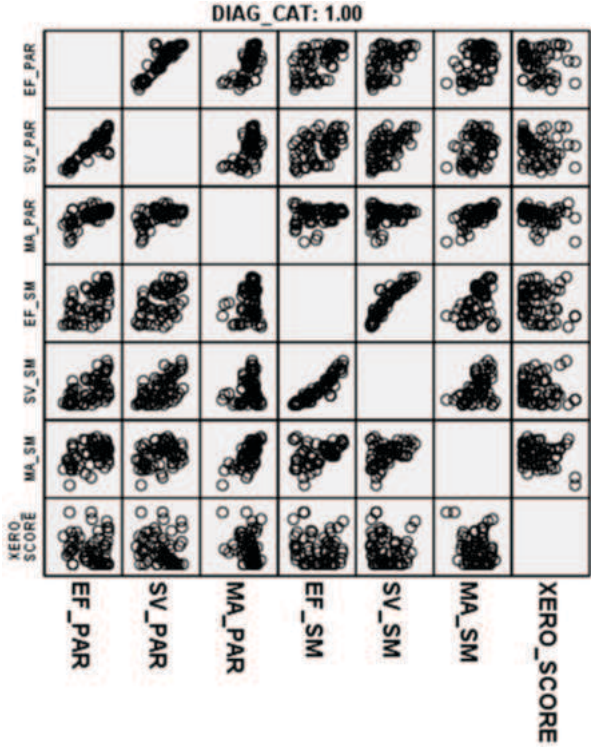


Figure 7- Scatter Plot Depicting Correlation Of Quantitative Parameters And Xerostomia Scores In Patients With Primary Sjögren's Syndrome (pss).

Table 6-scatter Plot Depicting Correlation Of Quantitative Parameters And Xerostomia Scoresin Patients With Primary Sjögren's Syndrome (pss)4

	Excretion fraction in parotid	Secretion velocity in parotid	Maximum accumulation in parotid	Excretion fraction in submandibular	Secretion velocity in submandibular	Maximum accumulation in submandibular	Xerostomia Score
Excretion fraction in parotid		0.893**	0.677**	0.584**	0.565**	0.407**	-0.210
Secretion velocity in parotid	0.893**		0.563**	0.466**	0.595**	0.296*	-0.234
Maximum accumulation in parotid	0.677**	0.563**		0.266**	0.250	0.692**	-0.344**
Excretion fraction in submandibular	0.584**	0.466**	0.266*		0.921*	0.441**	-0.162
Secretion velocity in submandibular	0.565**	0.595**	0.250	0.921**		0.444**	-0.127
Maximum accumulation in submandibular	0.407**	0.296*	0.692**	0.441**	0.444**		-.0244
Xerostomia score	-0.210	-0.234	-0.344**	-0.162	-0.127	-0.244	

** - Correlation is significant at the 0.01 level (2-tailed)
* - Correlation is significant at the 0.05 level (2-tailed).

A correlation was performed between quantitative parameters of parotid and submandibular glands & xerostomia score using Pearson correlation. There was no statistically significant correlation between quantitative parameters and the xerostomia score although xerostomia score had a negative correlation between all the quantitative parameters of both parotid and submandibular salivary glands. However, there was statistically significant positive correlation (r = 0.893) between EF % of parotid and SV % of parotid glands. Also, there was there was statistically significant positive correlation (r = 0.921) between EF % of parotid and SV % of submandibular glands.

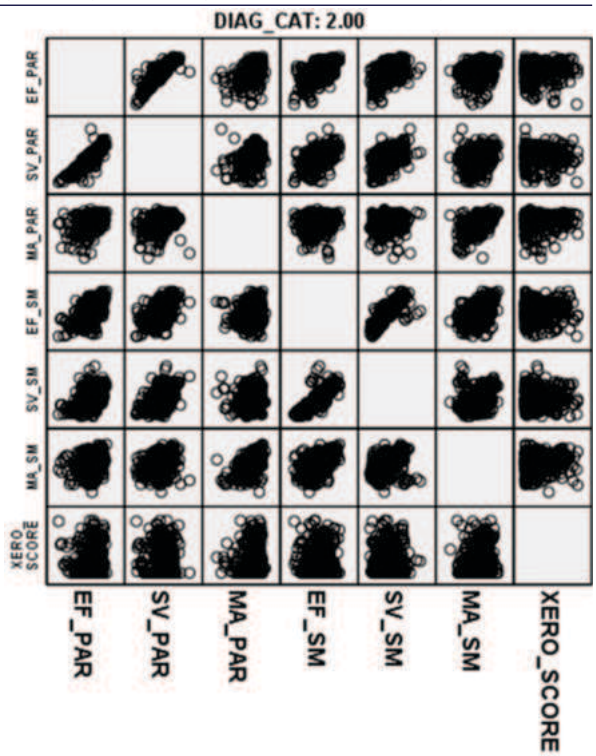


Figure 8-scatter Plot Describing Correlation Of Quantitative Parameters And Xerostomia Scores In Patients With Secondary Sjögren's Syndrome (sss)

Table-7 Scatter Plot Depicting Correlation Of Quantitative Parameters And Xerostomia Scores In Patients With Secondary Sjögren's Syndrome (sss)

	Excretion fraction in parotid	Secretion velocity in parotid	Maximum accumulation in parotid	Excretion fraction in submandibular	Secretion velocity in submandibular	Maximum accumulation in submandibular	Xerostomia Score
Excretion fraction in parotid		0.863**	0.431**	0.565**	0.443**	0.252**	0.060
Secretion velocity in parotid	0.863**		0.311**	0.527**	0.510**	0.214**	0.006
Maximum accumulation in parotid	0.433**	0.311**		0.148*	0.135*	0.516**	0.110
Excretion fraction in submandibular	0.565**	0.527**	0.148*		0.816**	0.431**	0.047
Secretion velocity in submandibular	0.443**	0.510**	0.135*	0.816**		0.251**	0.005
Maximum accumulation in submandibular	0.252**	0.214**	0.516**	0.431**	0.251**		0.076
Xerostomia score	0.060	0.006	0.110	0.047	0.005	0.076	

** - Correlation is significant at the 0.01 level (2-tailed).
* - Correlation is significant at the 0.05 level (2-tailed).

A correlation was performed between quantitative parameters of parotid and submandibular glands & xerostomia score using Pearson correlation. There was no statistically significant correlation between quantitative parameters and the xerostomia score although xerostomia score had a negative correlation between all the quantitative parameters of both parotid and submandibular salivary glands. However, there was statistically significant positive correlation (r = 0.863) between EF % of parotid and SV % of parotid glands. Also, there was there was statistically significant positive correlation (r = 0.816) between EF % of parotid and SV % of submandibular glands.

DISCUSSION

The mean age (SD) in cases was 42.34 (11.64) years and controls 40.97 (12.79) years with no statistically significant difference p = 0.996. Females were more affected than males. There was no significant statistical difference in gender distribution between the cases and controls; p = 0.428.

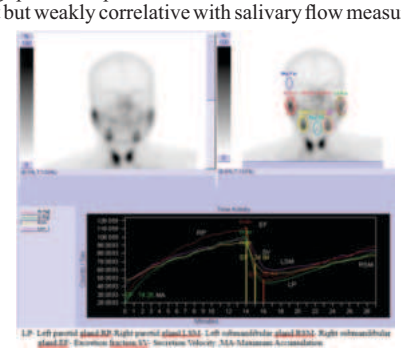
Coming to the cases, the majority of the participants almost 57% of the total participants were either suspected or confirmed cases of SSS referred for SGS. This was because the prevalence of SSS is more frequent than the primary counterpart described previously.[2,3,4,5,12]

The SGS quantitative parameters of parotid glands such as EF% and

SV% have statiscally significant difference between cases and controls ($p < 0.001$ and $p = 0.001$ respectively). Quantitative parameterMA_{15}% of parotid did not show any statistical significant difference between cases and controls ($p = 0.285$). The SGS quantitative parameters of submandibular glands namely EF%, SV% and MA_{15}% have shown statistical significant difference between cases and controls ($p = 0.008$, $p = 0.012$ and $p = 0.034$ respectively). These findings were remotely similar to the study conducted by Booker et.al. where they found that decreased parotid to submandibular gland uptake ratio to be a statistically significant indicator of salivary dysfunction, and also, parotid EF% > 50 was found to indicate normal salivary function. The above findings in the study were also in stark contrast to the two separate articles published by Aung W et.al.[13,14] where they have found that along with reduced Maximum-Secretion (MS) and Secretion-Velocity (SV) they observed reduction in Maximum-Accumulation (MA) in all the salivary glands. The MA parameter was similar to that of the MA_{15} parameter in our study. On comparison of quantitative parameters between and within groups of PSS, SSS and healthy controls there was statistically significant difference was seen in EF% and SV % of parotid glands ($p < 0.001$ and $p < 0.001$ respectively) and EF% and SV% of submandibular glands ($p = 0.02$ and $p = 0.024$ respectively). The quantitative parameters MA_{15} % in both parotids ($p = 0.187$) and submandibular glands ($p = 0.779$) did not show any statistical significant difference between PSS, SSS and healthy controls.

Coming to the xerostomia score, there was a huge variation in patients, mean$\pm$ SD xerostomia score being 17.30 ± 18.67. This was due to the fact many of the cases had xerostomia score of zero when assessed at the time of procedure leading to the wide dispersion of the xerostomia score, causing erroneous results. For the first time, the utilisation of XQ to correlate with salivary gland functional parameters has been performed. The patient self-reported xerostomia by XQ.[6] has been adopted because it was better correlating with stimulated & non-stimulated salivary flow rates than observer-rated RTOG/EORTC scoring grade, which was observed in a study conducted by Amichay Meirovitz.[15] et al. Siavash J et.al.[16] also carried out a study where they have validated XQ in head-and-neck cancer patients with intensity-modulated RT (IMRT) compared with patients who received standard radiotherapy (RT). They showed that XQ was valid and reliable to evaluate xerostomia. During the study, the patients were finding it difficult to understand and report the scores based on XQ.[15] this may have led to the false interpretation of the patient problem thereby leading to an untrue representation of the data. Further studies are required to evaluate the effectiveness and validate the patient self-reported XQ in SS. An effort has to be made to invent a more simplified, yet robust XQ so that patient will be at ease to report the problems and avoid the subsequent discrepancies.

In the study, the correlation between the xerostomia score and SGS quantitative parameters in cases was not statistically significant ($p > 0.05$) or correlative ($r < 0.7$) (either positive or negative). And also, there was no statistically significance ($p > 0.05$) or correlative (either positive or negative) ($r < 0.7$) between SGS quantitative parameters and xerostomia score in patients with PSS and SSS. However, there was statistically significant positive correlation between EF% and SV% of parotid glands ($r = 0.872$) and between EF% and SV% of submandibular glands ($r = 0.841$) in cases. Statistically, a significant positive correlation was found between EF% and SV% of parotid glands ($r = 0.893$) and between EF% and SV% of submandibular glands ($r = 0.921$) in PSS. Similarly, a statistically significant positive correlation was observed between EF% and SV% of parotid glands ($r = 0.863$) and between EF% and SV% of submandibular glands ($r = 0.816$) in SSS. The correlation was higher in PSS patients than SSS patients. The above results were similar to a study conducted by Avraham Eisbruchet al.[6] They found out XQ to be reliable and valid in measuring patient-reported xerostomia which was statistically significant but weakly correlative with salivary flow measurements.



Figures 9- Showing Salivary Scintigraphy In Participants.

Curves are obtained after drawing region of interest around each salivary gland with background. In subjects with normal functioning parotid and submandibular glands there is rise in the curve (tracer accumulation) followed by a steep fall after sialagogue administration. The gland again accumulates tracer after sialagogue effect.

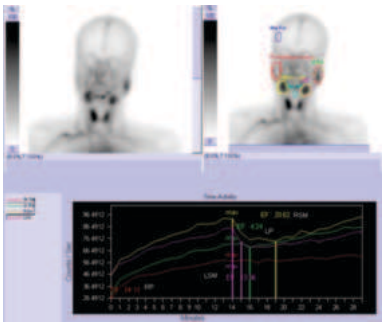


Figure 10- salivary Scintigraphy Showing Severely Affected Bilateral Parotid And Submandibular Glands.

Curves are obtained after drawing region of interest around each salivary gland with background. In subjects with severely affected parotid and submandibular glands there is rise in the curve (tracer accumulation) followed by a very minimal fall or a continuous flat curve or an upsloping curve after sialagogue administration. The excretion function of the salivary glands is affected leading to the above mentioned curve pattern.

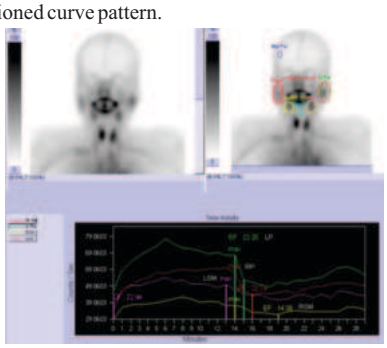


Figure 11- Salivary Scintigraphy Showing Moderately Affected Bilateral Parotid And Submandibular Glands.

Curves are obtained after drawing region of interest around each salivary gland with background. In subjects with moderately affected parotid and submandibular glands there is rise in the curve (tracer accumulation) followed by a moderate fall after sialagogue administration. The gland again accumulates the tracer gradually after sialagogue effect.

CONCLUSIONS

In conclusion, the study compared the quantitative parameters of salivary scintigraphy between 167 cases and 75 healthy controls. Quantitative parameters such as Excretion-Fraction % and Secretion-Velocity % in parotid glands and Excretion-Fraction %, Secretion-Velocity % and Maximum-$Accumulation_{15}$% in submandibular glands were statistically significant between the two groups. However, there was no statistically significant correlation between xerostomia-score derived from Xerostomia-Questionnaire and quantitative parameters derived from salivary scintigraphy in cases. Therefore it can be said that the quantitative parameters (EF %, SV %) in parotid glands (EF %, SV % and MA_{15} %) in submandibular glands may be considered to be sensitive parameters in the assessment of salivary gland function in cases of primary and secondary Sjögren's syndrome. Also, further studies have to be done to validate xerostomia questionnaire in patients affected with Sjögren's syndrome and to correlate with quantitative parameters of salivary scintigraphy.

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