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RESEARCH ARTICLE

ROLE OF ESTROGEN RECEPTORS AS PROGNOSTIC TOOL IN CHRONIC SINUSITIS

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Abstract: ***Background:*** Chronic Rhinosinusitis (CRS) is a common condition which causes disease burden worldwide affecting at least 11 % of the global population. There have been studies which show the correlation with action of estrogen receptors in nasal mucosa and their actions. This current study aimed to prove that estrogen receptors can be used as a reliable biomarker for prognosis of CRS. ***Methodology:*** In this control study, 100 patients who came to our Outpatient Department were diagnosed to have CRS according to European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) criteria. Patient had nasal swabs taken before and after treatment and the estrogen receptors were measured and the results were noted. The study was done in SRM medical college and hospital. ***Results:*** As per our study, most of the patients were in 40-49 group (21.6%).The study showed that group A had higher female population (60% female and 40% male), while Group B showed more male population (55% male and 45% female) and in group C there was equal distribution (50% male and 50% female). Overall, 52.5% female and 47.5% male presented with chronic sinusitis in our study.In group A, where medical treatment was given ERβ showed a significant decrease post treatment (77%) while no changed noted in ERα (4%).In B group, where surgical treatment was given ERβ showed a significant decrease post treatment (83%) while there was no significant change in ERα (19.7%). ***Conclusion:*** ERβ is a more sensitive prognostic tool for chronic sinusitis. Further research should be done to harness the pharmaceutical properties to give a specific and tailored treatment for chronic sinusitis. These results suggest that ERβ may be instrumental in predicting disease progression and treatment outcomes, providing a new avenue for personalized therapeutic strategies. Furthermore, understanding the involvement of estrogen receptors in CRS pathophysiology could pave the way for targeted pharmaceutical interventions to enhance treatment efficacy. This study is genetic study done with RTPCR.It helps to understand the correlation between estrogen receptors and chronic sinusitis.In my study, we found that estrogen receptor beta decreased after treatment.

Keywords: Chronic sinusitis, Estrogen Receptors, Nasal Swab, RTPCR

INTRODUCTION

Chronic sinusitis is the most common disease seen in nasal cavity affecting atleast 11% of global population.[1].There have been studies which show the correlation with action of estrogen receptors in nasal mucosa and their actions. This current study aimed to prove that estrogen receptors can be used as a reliable biomarker for prognosis of CRS.

Chronic sinusitis is defined as inflammation of sinonasal cavity due to bacterial infection with clinical symptoms that last for more than 12 weeks. The most common bacterial pathogens are Streptococcus pneumoniae (20-43%), Haemophilus influenzae (22-35%), Moraxella catarrhalis (2-10%), and Staphylococcus aureus (0-8%). The symptoms include block in nose and obstruction, discharge from nose, headache, and heaviness of face.

According to the EPOS [2] (European position paper on rhinosinusitis and nasal polyps) criteria, Rhinosinusitis was defined as inflammation of mucoperiosteal lining of paranasal sinus for more than 12 weeks with or without nasal polyposis (figure 1).

Figure 1 Shows nasal endoscopy with polyp. Image taken from our department.

Additionally, patient should have any 3 of the following ,discoloured discharge (unilateral>bilateral),severe pain (unilateral predominance),fever, elevated CRP/ESR and double sickening- deterioration after initial milder phase of illness.Phenotypically divided into Chronic sinusitis with polyp (CRSwNPs) and Chronic sinusitis without polyp (CRSsNPs)

CT scans (figure 2) are now the standard for imaging paranasal sinuses, replacing conventional radiographs assessment of sinusitis. While indications are similar to nasal endoscopy, both methods should be used complementarily. Repeat CT scans might be necessary if nasal endoscopy shows limited findings, but ongoing disease is suspected. CT scans excel in detailing bone structure and detecting minor mucosal swelling, aiding in operative planning and guiding surgery.

Figure 2 CT scan showing polypoidal changes in right maxillary sinus. Image adapted from our department

Magnetic resonance imaging (MRI) can be a useful adjunct to CT scans, but it is more expensive and time consuming. Any tumours in the soft tissue and intracranial complications can be seen in MRI. Soft tissue architecture is seen well in MRI but not structure of bone MRI also assessed fluid of different components and scarring tissue can be seen more easily

The first line of management is medical treatment.[3] As the mucosal lining becomes unsterile with bacterial invasion, oral and intravenous antibiotics should be given. Antihistamines are also given to reduce the mucous production and allergic symptoms. The other medical treatment that can be given is steroids both local and systemic form as it helps in reducing inflammation and congestion of nose and promotes drainage of OMC. Saline nasal douching can also be given as it helps improve clearance and promotes ciliary activity.

Surgical treatment is Functional Endoscopic Sinus Surgery (FESS) in which all the involved sinus openings should be widened or opened to facilitate drainage.[4] FESS can be clubbed with other surgeries like septoplasty to remove any anatomical deformities.

Our aim of this study to establish if estrogen receptors can be used as a prognostic marker for chronic sinusitis and to establish the levels of estrogen receptor. Our main objective was to ascertain the role of estrogen receptors as a prognostic tool in chronic sinusitis and to compare the levels of estrogen receptors before and after treatment of chronic rhinosinusitis

MATERIALS AND METHODS

Type Of Study: Case control study

Place Of Study: Department of Otorhinolaryngology and Head and Neck surgery.
Study Period: 2 years
Study Population**:** All patients who report to the ENT OPD with features suggestive of chronic sinusitis who fulfill inclusion criteria
Study Size: All patients with findings suggestive of chronic sinusitis attending Otorhinolaryngology, Head and Neck Surgery Outpatient Department. n = 100

INCLUSION CRITERIA

- 18-70 years of age
- All patients of chronic sinusitis who fill EPOS criteria, i.e Presence of 2 or more symptoms, one of which should be either nasal block/obstruction/congestion or nasal discharge +/- facial pain, anosmia/hyposmia for more than 12 weeks with endoscopic findings of polyps/ mucopurulent discharge primarily from middle meatus and/or edema/mucosal obstruction primarily in middle meatus
- Patients having symptoms of more than 12 weeks

EXCLUSION CRITERIA

- Patient of age group less than 18 and more than 70
- Children have less incidence of sinusitis
- Symptoms of less than 12 weeks
- Patients having symptoms of allergic rhinitis
- Hyper estrogen states like pregnancy, menstruation, polycystic ovarian syndrome, patients on hormone replacement therapy and carcinoma of ovaries, endometrium
- Hypo estrogen states like menopause, inborn errors of steroid metabolism
- Patients not willing for the study

GROUPING :

After obtaining ethics clearance Ethics ID :xxxIEC-ST0224-1453
Patients are split into 3 groups according to a severity index based on a scoring system called snot 22 questionnaire. (Figure 4)
Group A- patients having symptoms of rhinosinusitis and will be given medical treatment
Group B-patients having symptoms of rhinosinusitis and will be given surgical treatment based on the severity score and patients where medical treatment has failed
Group C-healthy population

S.no	Symptoms	No problem	Very mild problem	Mild or moderate problem	Moderate problem	Severe problem	Problem as bad as it can be
1		0	1	2	3	4	5
2		0	1	2	3	4	5
3		0	1	2	3	4	5
4		0	1	2	3	4	5
5		0	1	2	3	4	5
6		0	1	2	3	4	5
7		0	1	2	3	4	5
8		0	1	2	3	4	5
9		0	1	2	3	4	5
10		0	1	2	3	4	5
11		0	1	2	3	4	5
12		0	1	2	3	4	5
13		0	1	2	3	4	5
14		0	1	2	3	4	5
15		0	1	2	3	4	5
16		0	1	2	3	4	5
17		0	1	2	3	4	5
18		0	1	2	3	4	5
19		0	1	2	3	4	5
20		0	1	2	3	4	5
21		0	1	2	3	4	5

22		0	1	2	3	4	5

Table 1: SNOT Questionnaire. Adapted from A study of SNOT 22 scores in adults with no sinonasal disease

SNOT 22 QUESTIONNAIRE: 8-20 mild, >20-50 moderate, and >50 severe

Nasal swabs will be sent from these 3 groups to see estrogen receptor levels (normal range is 3-1000 fmol/mg of protein) Treatment will be given for rhinosinusitis and after 1 month a repeat nasal swab will be sent and estrogen receptors levels will be noted

TESTING FOR NASAL SWAB

Storage And Transport Of Sample

- Nasal swab was taken from nasal mucosa pretreatment and sent to our lab for RTPCR testing
- The swab was stored in 1 mL Invitrogen TRIzol reagent in Eppendorf tubes which is a ready to use reagent designed to isolate high quality data from cell tissues samples of human.
- It maintains the integrity of RNA due to highly effective inhibition of RNase activity while disrupting the cells and dissolving cell components.
- The steps are done in room temperature. After wearing disposable gloves, RNaseZap decontamination solution is used to remove contamination in the worksurface.

Isolate rna:

- 0.5ml of isopropanol is added to aqueous plane and incubated for 10 minutes at 4ºC
- The sample is then centrifuged for 10 minutes at 12,000 x g at 4ºC and the total RNA precipitate forms a white gel like pellet at the bottom of the tube. The supernatant is then discarded.
- The pellet is then resuspended in 1ml of 75% of ethanol per ml of TRIzol and the supernatant is then discarded. The pellet is then air dried or vacuumed.
- The pellet is then resuspended in 20-50 µL of RNase-free water by pipetting up and down and then incubated in water bath or heat block set at 55º-60ºC for 10-15 minutes.

RTPCR Of The RNA**:**

- For this step High-Capacity c DNA kit was used and the kit components were allowed to thaw on ice. The volume of components needed to prepare the required number of reactions are mixed.
- 10 µL of 2X RT master is pipetted into and mixed into each well of a 96-well reaction plate or individual tube. 10 µL of RNA sample is pipetted into each well, pipetting up and down two times to mix.
- The plates are then sealed and centrifuged to remove air bubbles. The thermal cycler are then programmed to a reaction volume of 20 µL .
- The reaction plates are loaded into the thermal cycler and the machine is then run and values noted.

Table 2: Primer sequences of various genes used for qPCR

Gene Name	Primer Sequence
ER alpha	Forward-ACACCTGAGGGAAGAGAGTATTA Reverse-GACTCAAACTTGGCTGCTTTAC
ER beta	Forward-ACCGTGTGTGATGTCCTAATC Reverse-GTCCCAAGAGGGTGTCATTT
beta Actin (ACTB)	Forward- GCTAAGTCCTGCCCTCATTT Reverse - GTACAGGTCTTTGCGGATGT

Descriptive statistics is given by frequency, graphs, mean ± SEM and percentages and analytical statistics is given by unpaired t-test to see relationship between two categorical variables. P - value<0. 05 is considered to be significant throughout the study.

RESULTS AND OBSERVATIONS:

Table 3: shows age distribution among the research population.

Age	Frequency	Percentage	Min-Max
<20	8	13.3%	15-67
20-29	12	20%	
30-39	11	18.3%	
40-49	13	21.6%	
50-59	10	16.6%	
60-69	6	10%	

The study revealed that the majority of patients were in 40-49years age group (21.6%) followed by 20-29years (20%) and then 30-39years (18.3%) while the smallest proportion was made by 60-69years group(10%). (table 1)
The study showed that group A had higher female population (60% female and 40% male), while Group B showed more male population (55% male and 45% female) and in group C there was equal distribution (50% male and 50% female). Overall, 52.5% female and 47.5% male presented with chronic sinusitis in our study. (table 2)

Table 4: shows gender distribution among study groups.

GROUP	MALE	FEMALE	
Group A	60%	40%	Overall Male: 52.5% Female: 47.5%
Group B	45%	55%	
Group C	50%	50%	

In group A, where patients of chronic sinusitis were treated with steroid sprays and antihistamine, the levels of ERβ were significantly reduced post treatment from 1.38 to 0.31.

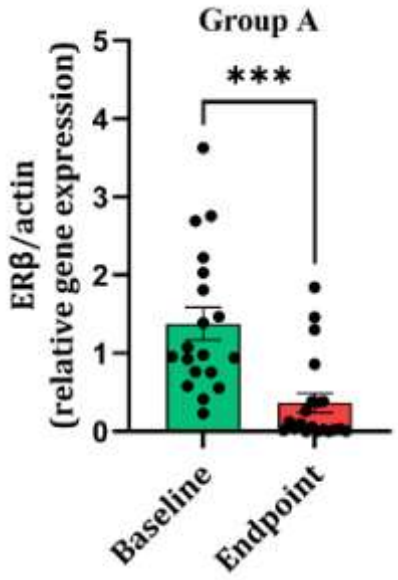

Figure 3: *Graph showing the levels of ER beta gene expression pre and post treatment in Group A patients. Data represented as Mean ± SEM. ***p < 0.001 compared with baseline data set.*

In the same group, there was no significant changes in ER α and the values remained almost same pre and post treatment (0.82 pretreatment and 0.78 posttreatment).

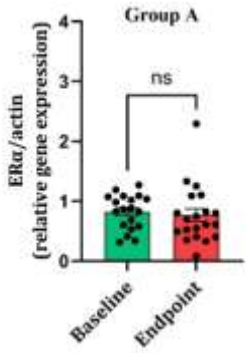

Figure 4: Graph showing the levels of ER alpha gene expression pre and post treatment in Group A patients. Data represented as Mean ± SEM. ns p > 0.05 compared with baseline data set.

In group B, who were patients of chronic sinusitis treated surgically, there was a significant decrease of ERβ post-surgery (0.96 pretreatment and 0.16 posttreatment).

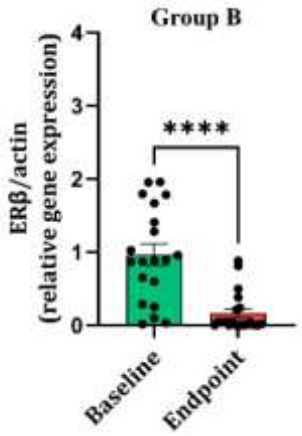

Figure 5: Graph showing the levels of ER beta gene expression pre and post treatment in Group B patients. Data represented as Mean ± SEM. ****p < 0.0001 compared with baseline data set.

But in patients of group B, there was no significant change in ER α post-surgical treatment (0.71 pretreatment and 0.85 post treatment). This indicates that ERβ plays a more significant role in the physiology of nasal mucosa.

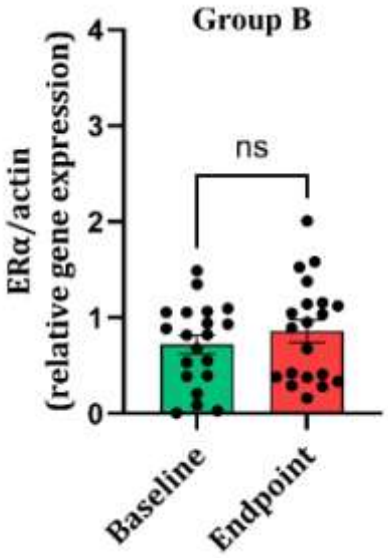

Figure 6: Graph showing the levels of ER alpha gene expression pre and post treatment in Group B patients. Data represented as Mean ± SEM. ns p > 0.05 compared with baseline data set.

In group C, which were healthy patients, the range was found to be 0.2-0.18 in males and 0.5-2.1 in females. As per our study, the majority of patients were in 40-49 age group (21.6%).The study showed that group A had higher female population (60% female and 40% male), while Group B showed more male population (55% male and 45% female) and in group C there was equal distribution (50% male and 50% female). Overall, 52.5% female and 47.5% male presented with chronic sinusitis in our study.In group A, where medical treatment was given ERβ showed a significant decrease post treatment (77%) while there was no significant change in ERα (4%). In group B, where surgical treatment was given ERβ showed a significant decrease post treatment (83%) while there was no significant change in ERα (19.7%).

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DISCUSSION

Chronic sinusitis is a debilitating disease that causes global burden. Estrogen receptors has already been found to be useful prognostic market in breast cancer. This study was done to see if estrogen receptors is a good prognostic tool for chronic sinusitis.

In our study, majority of the patients were in the age group 40-49 (21.6%) with a mean age of 46.50±14.16 which correlates with a study done by Shashy et al.[5] Overall, 52.5% female and 47.5% male presented with chronic sinusitis in our study, aligning with a study done by Ference et al.[6] Noticeably females are more

likely to present with symptoms of chronic sinusitis and get treatment as noticed with the previous study.

A study by Philpott et al. found that Progesterone and ERα receptors were absent in nasal biopsies, while ERβ receptors were present in the nasal mucosa of both males and females. as aligning with our study which shows a positive and statistically significant difference in ER beta values post treatment. [7]
According to a study done by Hideaki et al, turbinectomy was done for 7 patients and immunochemistry was done which showed ERβ found in five cases which also aligns with our study which shows a predominance of ERβ. [8]

In this study, there was no change in levels of ERα post treatment which correlates with a study done by Philpott et al. who said that progesterone and ERα do not act on nasal mucosa. This shows that ER beta can be used as a prognostic tool in chronic sinusitis while ER alpha does not play a significant role.

In a study done by Vaalima et al, the most common predominant estrogen receptor subtype seen in human oral epithelium and salivary glands was ER beta. [9]

This study shows that estrogen receptors plays an important role in the prognosis of chronic sinusitis and further studies should be done. Estrogen can also play an important role in the treatment of chronic sinusitis as it does in atrophic rhinitis

Overall, the strength in the study was noted to be the novel approach of this study, precise quantifications of estrogen receptors, proper statistical validation and the positive findings of ER beta being a potential prognostic marker for chronic sinusitis.

The limitations of the study was small sample size, single centre study, lack of long term follow up and there is a lack of understanding of the functional impact of estrogen receptors on sinus mucosa or disease progression.

CONCLUSION

This study highlights the potential role of estrogen receptor β (ERβ) as a sensitive prognostic biomarker in chronic rhinosinusitis (CRS).

The findings demonstrate a significant decrease in ERβ levels post-treatment in both medically and surgically managed groups, indicating its responsiveness to intervention. Conversely, ERα levels showed minimal variation, suggesting a lesser role in CRS prognosis.

These results suggest that ERβ may be instrumental in predicting disease progression and treatment outcomes, providing a new avenue for personalized therapeutic strategies. Furthermore, understanding the involvement of estrogen receptors in CRS pathophysiology could pave the way for targeted pharmaceutical interventions to enhance treatment efficacy.

Despite the promising insights, this study is limited by its relatively small sample size and single-center design, which may impact the generalizability of the results.
Additionally, the lack of long-term follow-up prevents a comprehensive understanding of the durability of ERβ as a prognostic marker. Future research should focus on larger, multi-institutional studies with extended follow-up periods to validate these findings.

Investigating the functional mechanisms of ERβ in sinonasal inflammation could further refine its clinical utility. Ultimately, integrating estrogen receptor analysis into CRS management may improve diagnostic precision and optimize patient-specific treatment approaches.

COMPLIANCE WITH ETHICAL STANDARDS:
There are no potential conflicts of interest. This study involved human participants and was done with their informed and written consent.

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