RELATION BETWEEN CHRONIC RHINOSINUSITIS AND SERUM VITAMIN D3 LEVEL

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ABSTRACT

Objectives:

To explore the relation between Chronic rhinosinusitis (CRS) and serum Vitamin D3 level.

Materials and methods:

A prospective, observational study consisting of 115 patients with CRS was carried out at Department of ENT & HNS in Bir Hospital from March 2018 to March 2019. Patients were divided into two groups: 'CRSwNP (Chronic rhinosinusitis with polyp)' and 'CRSsNP (Chronic rhinosinusitis without polyp).' Vitamin D3 levels were measured by Chemiluminescent Immunoassay method and compared between the two groups. Receiver operating characteristic (ROC) curve analysis was also performed to evaluate the role of vitamin D3 in discriminating between the two groups.

Results:

Out of 115 cases, 54 (47%) had CRSwNP and 61 (53%) had CRSsNP. Mean age of the patients was 34.7 years. Sixty six (57%) were female. Mean vitamin D3 level of all patients was 23.86 ng/ml. Only 17 (14.8%) patients had normal vitamin D3 level. CRSwNP patients had significantly lower vitamin D3 levels compared to CRSsNP patients (21.42 ng/ml vs. 26.01ng/ml respectively; p value <0.001). Higher proportion of patients with CRSwNP had Vitamin D3 deficiency compared to CRSsNP cases (35.2% vs. 16.4%). On ROC curve analysis of Vitamin D3 to discriminate CRSsNP from CRSwNP, area under the curve (AUC) was 0.718 and accuracy was 67.83% at a cutoff value of $\geq$ 23.15 ng/ml.

Conclusion:

The mean vitamin D3 levels in CRSwNP patients was significantly lower than CRSsNP patients. A cut off level of vitamin D3 level $\geq$23.15ng/ml had a fair ability to discriminate CRSsNP patients from CRSwNP patients.

Keywords: Chronic Rhinosinusitis (CRS), Polyp, Task force criteria, Vitamin D3.

INTRODUCTION

Chronic rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 weeks duration.[1] In 1996, the American Academy of Otolaryngology-Head & Neck Surgery (AAO-HNS) multidisciplinary Rhinosinusitis Task Force (RTF) provided case definition for CRS as consisting of at least 2 major factors or 1 major and 2 minor factors for more than 12 weeks. Major

factors included facial pain or pressure, nasal obstruction or blockage, nasal discharge or purulence or discolored postnasal discharge, hyposmia or anosmia, and purulence in nasal cavity. [2] The definition was later revised in 2002 by the Sinus Allergy Health Partnership (SAHP) Task Force to require confirmatory radiographic or nasal endoscopic or physical examination findings in addition to suggestive history.[1] Based on the presence or absence of nasal polyps, CRS is classified into CRS with polyps (CRSwNP) and CRS without polyps (CRSsNP).[1]

CRS is a major health problem with a prevalence of up to 10% in the USA and similar prevalence has been reported from Europe and Asia.[3,4] Despite the large impact of CRS, few population based studies have been conducted to elucidate the mechanism underlying inflammatory process in CRS. Research suggests that the etiology of CRS is complex and multifactorial and the concept of chronic mucosal inflammation has supplanted infection to describe this disorder, but this shift still neglects the issue of etiology.[3] One current hypothesis is that CRS results from a dysfunctional interplay between individual host characteristics and factors exogenous to the host.[5]

In recent years, many studies have investigated the role of vitamin D in the pathophysiology of chronic inflammatory respiratory disorders such as allergic rhinitis, chronic rhinosinusitis, and asthma.[6,7] Vitamin D derivatives have been shown to prevent proliferation of human nasal polyp-derived fibroblasts in cultured cell models and regulate activation of normal T cell expression and decrease secretion of Regulated on Activation, Normal T cell Expressed and Secreted (RANTES).[8,9] Several studies have shown that CRS patients suffer from vitamin D3 deficiency. Moreover, CRSwNP patients had lower vitamin D3 levels compared to CRSsNP patients in these studies.[10,11] A systematic review also found significantly lower Vitamin D3 levels in the polypoid phenotype of CRS compared to controls and that lower vitamin D3 levels were associated with an increased degree of inflammation.[12] Another study reported a significant dose dependent reduction in nasal polyp derived fibroblast proliferation after treatment with vitamin D3 in fibroblast cultures from patients with nasal polyposis. [13] In contrast, a study conducted by Apuhan et al involving 60 patients, found no statistically significant difference in vitamin D3 levels between CRSwNP patients and controls.[14] Thus the role of vitamin D in chronic rhinosinositis is still investigational. This study was therefore carried out to find out the level of serum Vitamin D3 in patients diagnosed with chronic rhinosinusitis and to assess whether there is any difference in vitamin D3 levels between CRSsNP and CRSwNP patients in Nepalese population.

MATERIALS AND METHODS

This prospective, observational, hospital based study was conducted at Otorhinolaryngology and Head & Neck Surgery Department of Bir hospital, National Academy of Medical Sciences, Kathmandu, Nepal from March 2018 to March 2019. Ethical approval was taken from Institutional Review board. One hundred and fifteen consecutive patients with chronic rhinosinusitis presenting to ENT-HNS outpatient department were selected for the study after obtaining informed written consent. The diagnosis of CRS was made as per AAO-HNS task force criteria[2] and SAHP Task force criteria[1] for chronic rhinosinusitis. Patients under Vitamin D3 supplementation, those with known abnormalities of Vitamin D3 metabolism and patients who did not give consent were excluded from the study.

Anterior rhinoscopy was done in all cases and Diagnostic Nasal Endoscopy (DNE) was performed when necessary for detection of polyps, discharge and edematous mucosa in the middle meatus. CT scan was requested when findings were non-confirmatory. On the basis of these examination, patients were divided into two groups: 'Chronic rhinosinusitis with nasal polyps (CRSwNP)' and 'Chronic rhinosinusitis without nasal polyps (CRSsNP).' Serum Vitamin D3 levels were compared between the two groups (CRSwNP and CRSsNP). Vitamin D3 level estimation was done by automated Chemiluminescent Immunoassay (CLIA) technology (VITROUS eci, Johnson and Johnson ortho clinical diagnostic) in biochemistry lab of hospital. Before the tests, the serum samples were kept in room temperature and required amount was taken from those tubes for vitamin D3 assessment. Vitamin D3 levels were defined as Sufficient (>30 ng/mL), Insufficient (21-29 ng/mL) or Deficient (<20 ng/mL) as per standard guidelines.[15] Those with insufficient or deficient Vitamin D3 levels were referred to Department

of Endocrinology for further evaluation and management. SPSS ver. 16.0 was used for data analysis. Continuous data has been expressed as mean ± SD and categorical data as proportions and percentages. Independent samples T test was used to compare continuous data. Chi square test was used for comparison of categorical data. ROC (receiver operating characteristic) curve analysis was performed to assess the utility of vitamin D3 in discriminating CRSsNP from CRSwNP cases and to find out the best cutoff value of Vitamin D3 with highest accuracy. A p value < 0.05 was taken as significant.

RESULTS

A total of 115 patients with chronic rhinosinusitis (CRS) were included in this study. Fifty-four (46.96%) cases had chronic rhinosinusitis with polyps (CRSwNP) and 61 (53.04%) had chronic rhinosinusitis without polyps (CRSsNP). Mean age of all CRS patients was 34.71 ± 13.73 years. In both the CRSwNP and CRSsNP groups, most patients were between 21-40 years (63% and 59% respectively). Mean age of CRSwNP cases was not significantly different than that of CRSsNP cases. Overall, sixty-six (57%) patients were female. CRSwNP group consisted of slightly higher proportion of females while the CRSsNP group had more males. However, the difference in gender distribution was not significant (Table 1).

Table 1. Age and gender characteristics

	CRS (n=115)	CRSsNP (n=61)	CRSwNP (n=54)	P value
Mean age (years)	34.71± 13.73	34.67± 15.15	34.76± 12.07	0.973
Male	49 (42.6%)	30 (49.18%)	19 (35.18%)	0.130
Female	66 (57.4%)	31 (50.82%)	35 (64.82%)	

Most common 'Major criteria' symptom among CRS patients was facial pain/pressure (92 patients, 80%) followed by nasal obstruction (78 patients, 67.8%). Headache (97 patients, 84.3%) was the most common 'Minor criteria' symptom. Higher proportion of CRSsNP patients complained of facial pain/pressure compared to CRSwNP patients (82.5% vs. 74.1%). However the difference was not significant. Incidence of purulent discharge and purulence on examination were significantly higher in CRSwNP cases compared to CRSsNP cases (p value of 0.005 and 0.012 respectively), (Table 2).

Table 2. Comparison of signs and symptoms between CRSwNP and CRSsNP cases

Sign/ Symptom		CRSwNP (N= 54) N (%)	CRSsNP (N= 61) N (%)	P value
Major Criteria	Facial Pain Pressure	40 (74.1%)	52 (85.2%)	0.187
	Facial congestion	26 (48.1%)	27 (44.3%)	0.736
	Nasal obstruction	40 (74.1%)	38 (62.3%)	0.177
	Purulent discharge	38 (70.4%)	28 (45.9%%)	0.005
	Hyposmia/ anosmia	12 (22.6%)	6 (10.0%)	0.067
	Purulence on examination	37 (68.5%)	27 (45%)	0.012
	Fever (acute)	4 (7.4%)	4 (6.6%)	0.858
Minor Criteria	Headache	47 (87%)	50 (83.3%)	0.579
	Fever (non-acute)	6 (11.1%)	5 (8.3%)	0.616
	Halitosis	3 (5.6%)	9 (14.8%)	0.107
	Fatigue	1 (1.9%)	7 (11.5%)	0.043
	Dental Pain	2 (3.7%)	7 (11.5%)	0.115
	Cough	18 (33.3%)	15 (25%)	0.327
	Otalgia/ Aural fullness	1 (1.9%)	3 (4.9%)	0.370

Mean vitamin D3 level in all CRS patients was 23.86 ng/ml. Mean vitamin D3 level in CRSwNP patients was significantly lower compared to CRSsNP patients (21.42 ng/ml vs. 26.01 ng/ml; p value < 0.001), (Table 3). Most patients with CRS [98 out of 115, (85.2%)] had insufficient or deficient vitamin D3 levels (< 30ng/ml). Only 17 (14.8%) patients with CRS had normal vitamin D3 levels. Significantly higher proportion of patients with CRSwNP had vitamin D3 deficiency compared to CRSsNP cases (35.2% vs. 16.4%). Similarly, vitamin D3 insufficiency was significantly more common in CRSwNP patients compared to CRSsNP patients (63% vs. 57.4%, p value $<$ 0.001). It is worth noting here that only 1 patient (1.9%) with CRSwNP had sufficient vitamin D3 level (Table 4).

Table 3. Mean Vitamin D3 levels in CRSwNP and CRSsNP cases

CRS type	N	Mean Vitamin D3 level (ng/ml)	p value <0.0001
CRSwNP	54	21.42 ng/ml ±5.52	
CRSsNP	61	26.01 ng/ml ±6.67	
Total (All CRS)	115	23.86 ng/ml ± 6.54	

Table 4. Comparison of Vitamin D3 levels in CRS cases and its subtypes

Vitamin D3 category (ng/mL)	CRS Total N (%)	CRSwNP N (%)	CRSsNP N (%)
Deficient (< 20)	29 (25.2%)	19 (35.2%)	10 (16.4%)
Insufficient (20-30)	69 (60.0%)	34 (63.0%)	35 (57.4%)
Sufficient (>30)	17 (14.8%)	1 (1.9%)	16 (26.2%)
Total	115 (100.0%)	54 (100.0%)	61 (100.0%)
P value < 0.001			

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the role of Vitamin D3 levels in differentiating CRSsNP patients from CRSwNP patients. The area under ROC curve (AUC) of Vitamin D3 level was 0.718, suggesting that it had a fair ability to discriminate CRSsNP from CRSwNP (Figure I). Best cutoff value of vitamin D3 for this purpose was ≥ 23.15 ng/ml. At this cutoff, accuracy was 67.8%. Sensitivity and specificity were 68.9% and 66.7% respectively. Positive predictive value and negative predictive values were 70% and 65.5%. Significantly higher proportion of CRSwNP patients had vitamin D3 levels < 23.15 ng/ml compared to CRSsNP patients (65.5% vs. 34.5%; p value < 0.001) (Table 5).

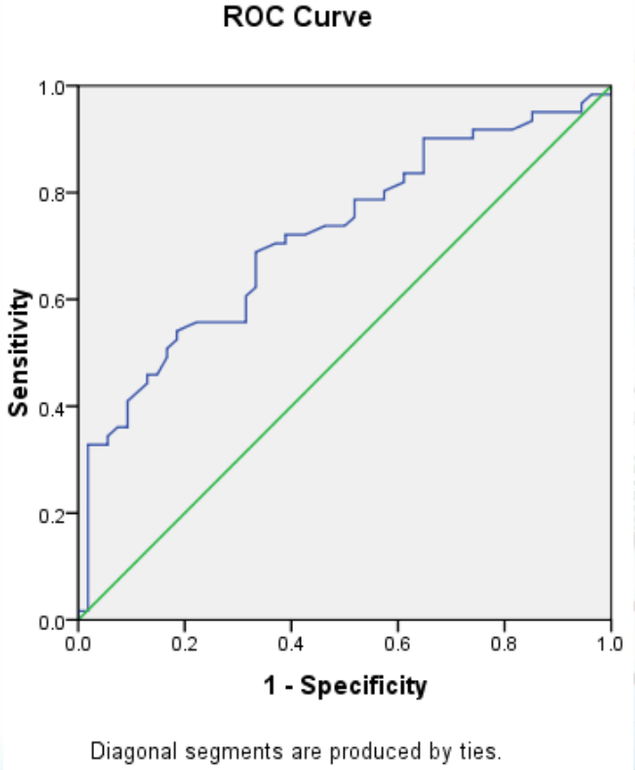

Figure I: ROC analysis of Vitamin D3 for discriminating CRSsNP and CRSwNP

Cut-off value of Vit D3	Area Under the Curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
23.15 ng/ml	.718	.047	.000	.625	.811

Note: The positive actual state is CRSsNP

Table 5.Vitamin D3 (at cutoff suggested by ROC) for differentiating CRSsNP vs. CRSwNP

		CRSsNP	CRSwNP	Total
Vit D3 level	≥ 23.15 ng/ml	42 (70%)	18 (30%)	60
	< 23.15 ng/ml	19 (34.5%)	36 (65.5%)	55
Total		61 (53%)	54 (47%)	115
Pearson chi square = 14.48; p value <0.0001				

DISCUSSION

Chronic rhinosinusitis (CRS) is a common disease that is associated with significant patient morbidity and socioeconomic burden. [4,16] In spite of this, few population-based epidemiologic studies have been conducted on its aetiopathogenesis and the mechanisms that drive inflammation in CRS still remain unclear. Recently, there has been growing interest in the role of Vitamin D3 in pathogenesis and treatment of CRS. However, there is a paucity of data in this regard from our region. So this study was conducted with the aim of investigating the association of serum Vitamin D3 levels with CRS and its subtypes in Nepalese people.

Our study consisted of 115 patients of chronic rhinosinusitis diagnosed as per AAO-HNS RTF and SAHP task force criteria. Among these, 54 (46.96%) had CRSwNP while 61 (53.04%) had CRSsNP. There was no significant difference in the age or gender distribution between CRSsNP and CRSwNP patients in our study. Our findings are

supported by most other studies. [11,17] In a recently published Indian study, most CRS patients were in the age group of 26-35 years and mean age of CRSwNP group was 35.67±11.24 and that of CRSsNP group was 32.50±11.82, which are similar to ours study. Moreover, they did not find significant difference in age or gender between CRSsNP and CRSwNP patients. [18]

Facial pain/pressure and nasal obstruction were the commonest major criteria symptoms reported by our CRS patients. Another study also had similar findings. [19] We noted that facial pain/pressure was more common in CRSsNP patients whereas nasal obstruction was more common with CRSwNP. Hulse et al also found that higher proportion of CRSsNP complained of facial pain/pressure [20] , meanwhile in another study, higher proportion of patients with CRSwNP presented with nasal obstruction/blockage compared to CRSsNP. [19]

The mean vitamin D3 level in our CRS patients (23.86 ng/ml) was below the normal range for vitamin D; 85.2% of our CRS patients had deficient or insufficient vitamin D3 levels. Due to high costs of Vitamin D testing and unethical financial burden to study subjects, control could not be taken in our study. In the absence of a control group, we could not ascertain whether the low level of Vitamin D3 in the present study was associated with CRS or simply a result of low vitamin D3 levels in general Nepalese population. Although there is lack of large population based studies of Vitamin D levels in Nepal, most available smaller studies indicate that Vitamin D deficiency may be common among Nepalese. A retrospective study of 108 children and adolescents from central Nepal found that 74.1% had Vitamin D levels < 30 ng/ml. [21] Another laboratory based study of 2158 subjects (19-60yrs) from Western Nepal also reported that 73.68% had vitamin D deficiency. [22] Meanwhile, at least three other studies have also reported that mean vitamin D3 level in both CRSsNP and CRSwNP patients were lower than the recommended level of ≥ 30 ng/ml for normal healthy individuals. [11,17,23]

Low levels of Vitamin D3 in CRS patients may be explained in view of the recently highlighted immunomodulatory role of vitamin D3 and better understanding of pathophysiology of CRS. Besides the traditionally recognized role of vitamin D3 in bone mineralization and calcium homeostasis [24], it has been now shown to have several important immunomodulatory, antiproliferative, and anti-inflammatory effects as well. [8,25] The VD3 receptor is found in several cell types within the immune system, including macrophages, antigen presenting cells, Th1 , Th2 , and regulatory CD4 + T cells. [12] Chronic rhinosinusitis is now considered to be a result of disordered inflammatory response. Both Th1 and Th2 cells have been demonstrated to have important roles in pathogenesis of CRS, although the extent of their roles vary between CRS subtypes. [26,27,28,29] Studies have shown that Vitamin D derivatives can prevent human nasal polyp-derived fibroblast proliferation in cultured cell models, and regulate activation of normal T cell expression. [8,9] Furthermore, a study has concluded that lower vitamin D levels were associated with higher degree of inflammation. [10]

It was seen in our study that mean vitamin D3 levels were significantly lower in CRSwNP patients compared to CRSsNP patients (21.42 ng/ml vs. 26.01 ng/ml); moreover vitamin D3 deficiency and insufficiency was significantly more common in those with nasal polyps. This is supported by several other studies. [23,30,31] A study from Taiwan reported that serum VD3 levels were significantly lower in patients with CRSwNP than in those with CRSsNP (21.4 +/- 5.7 vs. 28.8 +/-6.2 ng/ml; $p < 0.001$). In that study, incidences of vitamin D deficiency in CRSwNP and CRSsNP patients were 45.5% and 6.3% respectively. [11] An Indian study also reported that serum vitamin D3 levels were significantly lower in patients with CRSwNP (16.16±8.86) than in those with CRSsNP (23.28±5.35; p=0.001). In their study, 60% of CRSwNP and 20% of CRSsNP patients had vitamin D deficiency. Moreover, lower serum vitamin D3 was associated with higher polyp grade. [18] A retrospective study from USA also found that VD3 deficiency and insufficiency were more commonly found in CRSwNP patients. [10] A systematic review also found significantly lower VD3 levels in the polypoid phenotypes of CRS compared with controls and concluded that low VD3 levels were often associated with an increased degree of inflammation. [12] On the contrary, a study by Faghih Habibi et al did not find significant difference in vitamin D level between the CRSsNP and CRSwNP patients. [17] However, even their study has shown vitamin D level in CRSwNP to be lower than in CRSsNP patients. The reason for their results failing to reach statistical significance could be due to smaller sample size.

Table 6. Comparison of present study with other studies

Literatures	Vitamin D3 level (ng/ml)			P value
	CRSwNP	CRSsNP	Control	
Present study	21.42 ± 5.51	26.0 ±6.66	----	P<0.0001
Wang LF et al 2013[11])	21.4 ±5.7	28.8 ±6.7	----	P<0.001
Faghih Habib A et al 2019[17])	12.52	15.54	22.4	P=0.468
Sahni D et al 2019[18])	16.16 ±8.86	23.28 ±5.35	44.37 ±19.87	p=0.001
Wang F et al 2019[23])	15.28	19.25	21.64	P<0.001
Mulligan Jk et al 2011[30])	18±4	45±2	51±4	P<0.0001
Mostofa et al 2016[31])	13	50	51.6	P<0.001

The differences in vitamin D3 level between CRSwNP and CRSsNP patients may be due to distinct immune mechanisms underlying their pathophysiology. Current evidence suggests that CRSsNP and CRSwNP are unique disease entities associated with separate and distinct inflammatory mediator profiles within the sinonasal mucosa or mucus. [26] CRSsNP is predominantly characterized by mononuclear cell infiltration and exhibits a T-helper 1 cell (Th1) milieu. In contrast, CRSwNP is characterised by intense eosinophilic stroma and sub epithelial / perivascular inflammatory cell infiltration and appears to be associated with a typical T-helper 2 cell (Th2) skewed inflammation. [27] CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) are the end product of T-helper 1 (Th1) and Th2 cell skewing respectively. [28,29] Shahangia et al have recently explored the role of VD3 in pathogenesis of CRSwNP. According to them, sinonasal epithelial cells express 1-α-hydroxylase and can produce 1.25(OH)2 VD3 locally. Absence of this molecule leads to the reduced antibacterial response, increased release of inflammatory cytokines and increased fibroblast proliferation in patients with CRSwNP. [32] Therefore, as suggested by Wang LF et al, lower level of vitamin D3 in CRSwNP patients is a reflection of higher degree of inflammation in these patients. Additionally, polyp grades were found to have inverse relationship with serum vitamin D3 level. [11]

We further explored the utility of Viatmin D as a biomarker for discriminating CRSwNP from CRSsNP patients. ROC analysis showed that Vitamin D3 had a fair ability for this purpose. In our study, AUC of vitamin D3 was 0.718 and accuracy was 67.8% at a cutoff value of ≥ 23.15 ng/ml. A study from Romania found an AUC of 0.82 for discriminating those with CRS from those without. [33]

To the best of our knowledge, this is the first study to investigate the relation between serum vitamin D3 levels and CRS in Nepal. Although, vitamin D3 levels have been shown to be lower in CRS overall and in CRSwNP compared to CRSsNP, it remains to be seen whether there is a cause and effect relationship. Also, whether treatment with vitamin D3 is beneficial in CRS patients is still under investigation. Meanwhile, one study has proposed that CRSwNP patients should be screened for Vitamin D3 deficiency, and if insufficient (<30 ng/mL) supplementation with currently recommended doses be given.[34] In the future, randomized trials need to be carried out to establish a causal relationship for Vitamin D. Moreover, trials need also be directed towards evaluating the effect of Vitamin D supplementation in CRS patients. If positive results are confirmed, supplementation with Vitamin D may bring about a great change in management of these difficult cases.

We recognize that our study has some limitations. Firstly, a small sample size may limit generalization of the results. Secondly, we have not been able to eliminate all confounding factors for vitamin D levels. We did not have detailed information on geographical residence, ethnicity, socioeconomic status, lifestyle and dietary habits of participants, all of which might affect vitamin D levels. It is also possible that patients with severe CRSwNP might reduce their outdoor activities, leading to reduced sun exposure and hence lower vitamin D3 levels. Thirdly, nasal endoscopy and CT scan should have been ideally used as diagnostic tools in every case for confirmatory diagnosis of CRS since Task force criteria alone has limitation in diagnosing CRS and its subtypes. Finally, in the lack of a control group for comparison, we cannot definitely conclude whether low vitamin D levels in our CRS patients was specific to CRS

or simply a result of high prevalence of vitamin D deficiency in general Nepalese population.

CONCLUSION

Mean Vitamin D3 level in chronic rhinosinusitis and its subtypes is low in Nepalese population (23.86 ng/ml). The mean vitamin D3 level in CRSwNP patients was significantly lower than in CRSsNP patients (21.42 ng/ml vs. 26.01 ng/ml respectively; $p < 0.0001$). ROC curve analysis showed that Vitamin D3 level $\geq$ 23.15 ng/ml had a fair ability to discriminate CRSsNP cases from CRSwNP cases with an AUC of 0.718 and accuracy of 67.83%. More studies with larger samples need to be done to explore this association further.

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