



Chronic Lower Serum Calcium Levels and Globus Pharyngeus: Case Control Study

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ABSTRACT

Introduction: Globus is a persistent or intermittent, sensation of lump or foreign body in throat. It is long standing, difficult to treat and has tendency to recur. Numerous etiological factors have been postulated and the pathogenesis appears to be multifactorial. Thus, no protocols have yet been standardised for investigation and treatment options for globus. No earlier study had been found correlating globus with serum calcium levels.

Methods: A case control study of 32 patients conducted at a peripheral hospital in Bihar is hereby presented to compare serum calcium levels in globus patients and normal population. Mean values utilised as measures of central tendencies and t-test to evaluate the difference between these means.

Results: The case group was found to have mean serum calcium level (8.37mg/dl) lower than the normal reference range (8.5-10.5mg/dl) as well as the control group (8.99mg/dl) with significant P values (0.014).

Conclusion: Chronic low serum calcium levels may alter the normal function of esophageal muscles in globus. The serum calcium level of globus patients should be ascertained and corrected by supplementation if required.

Keywords: Globus pharyngeus, laryngoesophageal reflux, gastroesophageal reflux disorder, chronic hypocalcemia

time when Hippocrates first mentioned the term “globus” which in Latin means ball, the condition was considered to be associated with psychogenic factors or hysteria with such great belief that it was described by Oxford University Dictionary as “a choking sensation as of a lump in the throat to which hysterical persons are subject.” In 1968, a more accurate term “globus pharyngeus” to replace the existent “globus hystericus” was given by Malcomson.¹ Over the years numerous etiological factors have been postulated and a multifactorial role seems to be contributing towards the persistent nature. Thus, no protocol have yet been standardised for investigation and treatment options for globus. Studies have suggested role of gastroesophageal reflux and esophageal dysmotility in the origin of symptoms.²⁻⁴ A large portion of patients still do not present specific pathological abnormalities and remain symptomatic despite multiple treatment trials. The symptoms have been reported to persist for as long as two to seven years.⁵ The role of calcium and the effects of calcium levels on muscular tone and action is well known.⁶⁻⁹ The serum calcium levels thus, also play a role in pharyngeal and esophageal muscular activity. The aim of this study is to evaluate the association between chronic low serum calcium levels and globus pharyngeus. The literature review did not reveal any similar study in the past.

II. METHODS

This case control observational study was performed on outpatient basis in a peripheral hospital in Gaya (Bihar) involving a total of 32 patients. The globus pharyngeus case group

I. INTRODUCTION

Globus pharyngeus is a painless sensation of lump or foreign body in throat which may be intermittent or persistent. For ages, right from the



included the patients presenting with complaints of painless foreign body sensation, irritation, lump or stickiness in throat. A thorough history was taken to rule out previously proven cases of dysphagia, psychiatric illness, thyroid disease, calcium or other metabolic disorders. The patients were then examined clinically for oral cause, pharyngeal lesion or neck mass. Nasal endoscopy and laryngoscopy were performed to investigate structural, mucosal changes or signs suggestive of rhinosinusitis or gastroesophageal reflux. Barium swallow was occasionally requested in patients with difficulty swallowing and those with suspicion of malignancy. These patients were further evaluated by Computed tomography scans or Magnetic Resonance Imaging on case to case basis. Haemoglobin and serum calcium levels were done for the patients in whom no cause was elicited. Anaemic patients were excluded.

Due to limited resources, investigations like esophageal endoscopy, 24-hour dual probe ambulatory pH monitoring, multichannel intraluminal impedance monitoring or videofluoroscopy could not be made available.

Owing to the prevalent low nutrition state in the general population of this region of India, decision was made to include a control group in the

study. These individuals were randomly selected from the general outpatient department who presented with minor ailments and an informed consent was taken for inclusion in the study. The patients who did not consent for blood investigation or had any chronic illness or disorder affecting calcium metabolism were excluded. 16 patients each formed the case and control groups and mean values were calculated. The final observation was made by applying unpaired t-test to calculate P values for the mean serum calcium levels in case and control groups.

All patients diagnosed as hypocalcemic on testing were started on Proton pump inhibitors, calcium and Vit D3 supplementation and asked for monthly review. On follow-ups, symptomatic improvement was recorded and S. calcium levels were done.

III. RESULTS

Of the total 16 globus patients, 12 were female and 4 were male with age range from 22-54 years. Control group also comprised of randomly selected 16 patients and age range for control group was 25-60 years. (Table 1)

CASES	Number	Mean Age (in years)
Females	12	34.08
Males	4	38
CONTROLS	Number	Mean Age (in years)
Females	11	38
Males	5	40.2

Table 1: Age and Sex distribution

The sex distribution was comparable in both the groups. In the control group the average age was higher for both sexes.

Calcium level <9 mg/dl was seen in 12 patients and 5 controls. The mean serum calcium levels in case

group was found to be 8.37 mg/dl with a SD of 0.85 in comparison to the mean value 8.99mg/dl in control group with SD 0.34. (Table 2)

Group	Mean serum calcium levels (mg/dl)	SD
Case	8.37	0.85
Control	8.98	0.34

Table 2: Serum calcium in Case vs Control groups

On applying unpaired-t tests, P was found to be 0.014 which was significant.

FEMALE	Number	Calcium(mg/dl)
Cases	12	8.47
Controls	11	8.94
P value 0.035		



MALE	Number	Calcium(mg/dl)
Cases	4	8.08
Controls	5	9.08
P value 0.054		

Table 3: Comparison of S. calcium mean values between cases and controls in women and men

The mean calcium level was lower in cases compared to controls, in both sexes. The difference in mean calcium level of cases and controls was bigger in males, but p value was significant only among women (Table 3).

In the patients with globus, the men had lower calcium levels compared to women and the inverse was seen in controls.

S. Calcium(mg/dl)	Case	Control
<= 35 years	8.4	9.11
>35 years	8.33	8.86

Table 4: Age wise comparison of S. calcium levels in cases and controls

There were 9 cases and 8 controls aged 35 years and younger and they had a higher mean calcium level than those above 35 years of age. In both the age groups the mean calcium level was lower in the cases of globus (table 4). It is worth mentioning that controls had higher mean age than cases and this analysis shows that the higher calcium in controls cannot be explained by the age difference.

Some of the patients were lost on follow-up and others were inconsistent with their follow-up. Those who have been followed up at 3 months of starting oral calcium reported moderate improvement to complete absence of symptoms. However, the efficacy of the treatment cannot be ascertained with the small follow up data available in this study.

IV. DISCUSSION

Globus is a persistent or intermittent, sensation of lump or foreign body in throat. It is painless, long standing, difficult to treat and has tendency to recur.¹⁰ The patient may describe the sensation as a thread, hair, pin or ball stuck in throat which he or she finds it difficult to swallow. There is, however, no true dysphagia or odynophagia evident from the fact that patient does not give history of decreased appetite or food intake. The symptoms are reported by approximately 46% of apparently healthy individuals with peak incidence in middle age.¹¹ The incidence remains similar between male and female. In the past it has been termed as “globus hystericus” and thought to be a psychogenic complaint more commonly found in individuals with some form of hysteria. However, the

multifactorial etiology of the disease has been established and it has been more accurately termed as “globus pharyngeus”.

The symptoms of globus may arise due to various causes like- Gastroesophageal reflux disease (GERD), abnormal upper esophageal sphincter function, esophageal motor diseases, pharyngeal inflammatory causes (pharyngitis, tonsillitis, chronic sinusitis), upper aerodigestive malignancy, hypertrophy of base of tongue, retroverted epiglottis, thyroid diseases, cervical heterotrophic gastric mucosa, psychological factors and stress. The different investigations that help narrowing down the diagnosis and etiology are nasal, oral, laryngeal and esophageal endoscopic examination, Barium swallow, CT/MRI scan Videoflouroscopy, 24 hour dual probe ambulatory pH monitoring and 24 hour multichannel intraluminal impedance monitoring.

The mechanisms that presently thought to be the major factors contributing to the globus sensation are:

1. Direct irritation and inflammation of laryngopharynx by retrograde flow of gastric contents- Laryngopharyngeal reflux (LPR).¹⁴
2. Vagovagal reflex hypertonicity of Upper Esophageal Sphincter (UES) triggered by acidification or distension of distal esophagus.¹⁵
3. Hypertensive UES.¹⁶
4. Abnormal esophageal motility and bolus clearance in nonspecific esophageal motility disorders.⁴
5. Psychological and psychiatric disorders, and stress



Considering the multiple etiological factors makes it difficult to establish standard investigation and treatment strategies for globus patients.¹⁰ A study found that 14% of ENT specialists in United Kingdom performed no tests on globus patients but rather simply prescribed antacid medications if clinically indicated.¹² Apart from the pharmacological treatment aimed at reducing acid reflux and improving esophageal motility, other measures like Speech therapy, language therapy, laryngeal relaxation techniques, cognitive behavioural therapy and psychoactive/antidepressant drugs have been tried with varying success.¹³

The aerodigestive tract upto LES is composed of both skeletal muscles (pharyngeal muscles, laryngeal muscles, UES, upper esophagus) and smooth muscles (esophageal body, lower esophagus and LES). The role of calcium and the effects of calcium levels on muscular tone and action is well known.⁶⁻⁹ It is possible that the altered serum calcium levels may contribute to globus by the effect on these muscles but the abnormality evades detection by investigations since it acts more at the functional or molecular level rather than at structural level.

Serum Calcium is maintained within a fairly narrow range from 8.5 to 10.5 mg/dl (4.3 to 5.3mEq/L or 2.2 to 2.7mmol/L) in the human body. Normal values and reference ranges may vary among laboratories as much as 0.5mg/dl.¹⁷ Acute hypocalcemia may present as paraesthesia, fatigue, anxiety, muscle cramps, carpal spasms, cardiomyopathy, prolonged QT interval or life-threatening situations like bronchospasm and laryngospasm. Chronic hypocalcemia may, however be asymptomatic, only evident on laboratory findings. Abnormalities if evident may be in form of dry skin, coarse hair, brittle nails, dental caries, fatigue or mild psychoses. Changes in smooth muscle function with low serum levels of calcium may cause irritability of the autonomic ganglia and can result in dysphagia, abdominal pain, biliary colic, wheezing, and dyspnea.¹⁸

The chronically low serum calcium levels may subclinically affect the functioning of muscles of aerodigestive tract going unnoticed unless it presents as globus sensation. The skeletal muscles Cricopharyngeus, Thyropharyngeus fibres and upper esophageal muscles contribute towards the activity of UES. All three muscles may at times function to maintain tone in UES, however, only Cricopharyngeus contracts and relaxes in all physiological states consistent with UES.¹⁹ The UES does not have a basal tone and depends on active neural stimulation for contraction, however,

the tone generated varies depending on different factors like stress, vagal stimulation by esophageal dilatation and most prominent being the elasticity of Cricopharyngeus. This muscle has predominantly slow twitch fibres, increased sarcolemma, connective tissue and circular arrangement of fibres, all of which lead to its elasticity.¹⁹ Depleted calcium stores might lead to an abnormality in muscular relaxation which brings about the unusual sensation in the UES region perceived as globus by the patient. In a study by Corso et al, 28% of the 101 patients with increased UES tonic pressures had globus.²⁰

Smooth muscles have poor intrinsic stores of calcium and generally depend on extracellular calcium for contraction. Sims et al, have stated through their study that a rise in intracellular calcium concentration is important for initiating contraction of smooth muscles and calcium sensitisation involving RhoA kinase can sustain tension. Ca²⁺ sensitisation mediated by RhoA kinase pathway has an important role in contraction of esophageal muscles and LES tonic contraction.²¹ A continuous Ca²⁺ influx through cell membrane is involved in spontaneous tone production of LES, which thus, exhibit Ca²⁺ dependent resting tone and contractions.^{22,23} Abnormalities in LES contraction may lead to GERD, which is a known contributor to the genesis as well as aggravation of symptoms of globus.

Thus, serum calcium levels, in multiple ways, can contribute towards globus by altering functions at different levels of aerodigestive tract. In the present study, the case group had a mean serum calcium level less than the normal reference range. At this value (8.37mg/dl), the effects of hypocalcemia are not evident clinically in terms of parasthesias or muscle spasms of large muscle groups or carpal spasm, but smaller muscles like cricopharynx might suffer fatigue and functional abnormality leading to globus. Further, GERD and esophageal dysmotility may compound to aggravate globus. This, however, does not rule out the other causes but further consolidates multifactorial etiology of globus pharyngeus.

Men between 15 to 45 years of age have serum calcium levels 0.02 to 0.05 mmol/L (0.36 to 0.9 mg/dl) higher than women of the similar age and these values fall for both sexes during these 30 years. Serum calcium begins to rise in women after the age of 45 till 75 years.²⁴ In our study we found that mean calcium levels were higher in men with normal levels and in controls, but they were lower in cases and those with hypocalcemia. Women may become symptomatic earlier than men with falling



calcium levels, but our numbers are too low to confirm this gender difference.

Upper Esophageal sphincter dysfunction seems to be an appealing explanation for globus in absence of other causes. However, an investigation to validate the same is needed. It is advised that blood investigation to ascertain the calcium status of the globus patients may be requested along with other investigations and deficiency if any, should be corrected with calcium and Vitamin D3 supplementation. The patients in this study were planned for three months therapy with Proton pump inhibitors, calcium and Vit D3 supplementation and asked for monthly review. The follow up could not be satisfactorily maintained in all patients. Although, those who followed up for three months did claim relief in symptoms, but the number is not sufficient to remark in favour or against the observation in this study.

This study was limited by the small number of patients included in the analysis and the lack of follow-up. Corrected calcium and ionized calcium levels were not calculated, which may provide a better picture of the hypocalcemic status of the patients. Larger studies with consistent follow-ups are needed to elucidate the role of hypocalcemia in the etiopathogenesis of globus pharyngeus.

V. CONCLUSION

Globus pharyngeus is a disease of multifactorial etiology. The underlying mechanisms revolve around the abnormal muscular function of aerodigestive tract. Chronic low serum calcium levels may, in different ways alter the normal function of esophageal sphincter and body muscles in globus. The calcium status of globus patients should be ascertained and corrected by supplementation if required.

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