DOI: 10.7860/JCDR/2017/25571.10232

Original Article

Internal Medicine Section

Risk of GERD with Diabetes Mellitus, Hypertension and Bronchial Asthma – A Hospital based Retrospective Cohort Study

SITARA NANDYAL[1], SWETA SURIA[2], BHARTI CHOGTU[3], DIPANJAN BHATTACHARJEE[4]

ABSTRACT

Introduction: The rise in Gastro-Esophageal Reflux Disease (GERD) prevalence appears to have coincided with a simultaneous increase in the prevalence of diabetes mellitus, hypertension and bronchial asthma amongst the Indian population. Despite being evaluated extensively for their role as a risk factor for GERD, till date this relationship has remained a debatable one. Moreover, literature available on such studies conducted within Indian population remains scarce.

Aim: The aim of the present study was to examine the risk of developing GERD in patients suffering from diabetes mellitus, hypertension and asthma in a Southern Indian population. The present retrospective, triple cohort and hospital based study was conducted by accessing the patient records from the medical records department of a tertiary care hospital in Southern India.

Materials and Methods: The patient's records were accessed from the year 2011 onwards. Relative Risk (RR) was calculated to determine the risk of development of GERD with every disease. Chi-square test was used to determine the statistical significance of the relationship between each disease and the development of GERD. A p-value of <0.05 was considered statistically significant.

Results: In view of the time constraints as well as the limitations of the inclusion and exclusion criteria, data pertaining to only 40, 71 and 53 patients in Cohort 1 (diabetics), 2 (hypertensives) and 3 (bronchial asthmatics) respectively could be analyzed in the present study. The relative risk of GERD development was greater than 1 for patients belonging to Cohort 2 and 3, suggesting that the risk of GERD development is higher amongst hypertensives and asthmatics. Surprisingly, the diabetics (Cohort 1) were not associated with a high risk of GERD development. However, the relationship between any of the disease and GERD development was not statistically significant.

Conclusion: The present study found an increased risk of GERD development amongst patients suffering from hypertension and bronchial asthma, but not with diabetes mellitus.

Keywords: Gastro-esophageal reflux, Lifestyle diseases, Risk factors

INTRODUCTION

GERD is a common global health problem and it has been observed to be more prevalent among patients plagued by a slew of chronic disorders, among which diabetes mellitus [1,2], hypertension [3,4] and asthma [5,6] appear to figure prominently. Moreover, mechanistic theories for development of GERD based upon, for instance the intra thoracic pressure swings leading to the overriding of the lower esophageal sphincter pressure among asthmatics [7], peripheral neuropathy leading to autonomic dysfunction within the digestive tract along with the loss of Lower Esophageal Sphincture (LES) tone among diabetics [8], have lent credence to the notion that these diseases may possibly be intricately associated with GERD development. However, till date, the relationship between these three disorders and GERD remains a debatable one as the data so generated has been a conflicting one [9-12]. Moreover, our literature search revealed that majority of these studies have been conducted amongst the American and European population. Considering the sudden spike in the incidence of lifestyle disorders like diabetes mellitus [13], hypertension [14] and asthma [15] within the Indian population, GERD is no more a problem of the Western society and it needs careful evaluation amongst the Indian populace [16]. Hence, this study was conducted with the objective of examining the risk of developing GERD in patients suffering from diabetes mellitus, hypertension and asthma in a tertiary care hospital of Southern India.

Diabetes mellitus, hypertension and asthma are positively associated with the development of GERD; i.e., patients with diabetes mellitus, hypertension and asthma would possess a higher risk of developing GERD. Hence, the present study was undertaken to examine the risk of developing GERD in patients suffering from diabetes mellitus, hypertension and asthma in a Southern Indian population.

MATERIALS AND METHODS

The present study was designed as a triple cohort, retrospective, hospital based study. The necessary permissions were sought from the Institutional Ethical Committee and the medical records department of a tertiary care hospital in Southern India, for accessing the medical records of the patients fulfilling the inclusion and exclusion criteria. Identity of the patients, whose records were viewed and the details included in our study, were completely anonymous.

Patient records for years 2011-2015 were utilized for our study. Data extraction was initiated by accessing the patient logs of the year 2011. The records were screened and included into a study cohort as per the below mentioned inclusion and exclusion criteria.

Cohort 1 (Risk Factor-Diabetes Mellitus)

Inclusion criteria: Patients equal to or above 18 years of age diagnosed clinically with diabetes mellitus during or before 2011 (may or may not be receiving treatment).

The diagnosis of diabetes mellitus was additionally verified by the study investigator using World Health Organization (WHO) [17] and American Diabetes Association (ADA) criteria [18].

Exclusion criteria: Patients below 18 years of age. Patients with concomitant presence of co-morbidities like hypertension and bronchial asthma and GERD in 2011; may or may not be receiving treatment for the same.

Cohort 2 (Risk Factor-Hypertension)

Inclusion criteria: Patients equal to or above 18 years of age diagnosed clinically with hypertension during or before 2011 (may or may not be receiving treatment). The diagnosis of hypertension was additionally verified by the study investigator using WHO criteria [19].

Exclusion criteria: Patients below 18 years of age. Patients with concomitant presence of co-morbidities like diabetes mellitus and bronchial asthma and GERD in 2011; may or may not be receiving treatment for the same.

Cohort 3 (Risk Factor-Bronchial Asthma)

Inclusion criteria: Patients equal or above 18 years of age diagnosed clinically with bronchial asthma during or before 2011 (may or may not be receiving treatment). The diagnosis of bronchial asthma was additionally verified by the study investigator using Global Initiative for Asthma (GINA) 2014 criteria [20].

Exclusion criteria: Patients below 18 years of age. Patients with concomitant presence of co-morbidities; diabetes mellitus and hypertension along with GERD in 2011; may or may not be receiving treatment for the same.

Only those patients whose records had been updated either until December 31, 2015 or till the development of the study end-point, i.e., onset of GERD, were included within the study. This ploy helped counter the problem of missing data associated with retrospective studies. The data was extracted from the medical records in compliance with the proforma outlined in Appendix-1. The included patients were followed up from 2011 up to December 2015 or until the development of outcome; i.e., development of GERD (whichever was the earliest).

Keeping the alpha = 0.05, power of study = 80%, p (level of significance) = 0.05 (C.I. = 95%) and a hypothesized proportion equal to 0.225, a total of 390 patients, 130 patients in each cohort were to be included in this study.

STATISTICAL ANALYSIS

The qualitative results were expressed as frequency with percentages in parentheses. Quantitative data was expressed as mean±standard deviation. Chi-square test was employed to ascertain the significance of the relationship between each risk factor and development of GERD. RR was utilized to determine the risk of development of GERD with every disease. A p-value <0.05 was considered statistically significant.

RESULTS

Due to time constraints and the limitations imposed by the inclusion and exclusion criteria, only 164 patients could be included within our study, with the following distribution:

Cohort 1 (risk factor-diabetes mellitus); 40 (24.4%); Cohort 2 (risk factor-hypertension); 71 (43.3%) and Cohort 3 (risk factor-bronchial asthma); 53 (32.3%). The mean age of the overall study population was 57.57±15.97 years, with the gender distribution skewed towards males – 93 out of 164 (56.7% vs. 43.3% for females). The mean Body Mass Index (BMI) of the overall population was 24.02±5.5 kg/cm^2. In the period of observation from 2011-2015, 26 (15.9%) of the subjects developed GERD, with a mean time-span for GERD development from the onset of the first concomitant co-morbidity and second concomitant co-morbidity being 5.36±1.71 and 1.50±0.71 years respectively.

Cohort 1: The mean age of the subjects within Cohort 1 (patients with diabetes mellitus alone in 2011) was 61.15±12.97 years, with a gender distribution of 34 males (within cohort - 85%) and six females (within cohort - 15%). The mean BMI was 24.59±5.90 kg/cm^2. Among the 40 subjects in Cohort 1, 13 developed only bronchial asthma between the time period of 2011-2015. The mean time span for GERD development from the onset of the first (diabetes mellitus) and second disease (bronchial asthma) being 12.25±1.4 and 1.50±0.71 years respectively.

Only four of the 40 subjects (within cohort - 10%) in Cohort 1 developed GERD between the period of observation from 2011-2015. The RR of development of GERD amongst the Cohort 1 subjects when compared to the whole study population was 0.56, suggesting that the probability of development of GERD amongst the diabetics is less likely in comparison to the non-diabetics. However, a cross-tabulation evaluation of the overall Cohort 1 population using Chi-square test revealed that there was no statistically significant relationship between diabetes mellitus and GERD (p=0.244 for overall Cohort 1 population).

An evaluation of a subset (n=13) comprising of patients who developed bronchial asthma among the Cohort 1 subjects at a later stage, revealed the RR of development of GERD within this subset as 2.01. However, Chi-square test application did not reveal any statistical significance within this subset (p=0.431). Further, an analysis of the patients in Cohort 1 who did not develop bronchial asthma (n=27) revealed no statistically significant relationship between diabetes alone with development of GERD (p=0.564), with a RR of 0.48. This would suggest that though diabetes mellitus by itself may not be a risk factor for the development of GERD, the likelihood of development of GERD increases by almost two folds in diabetic patients developing bronchial asthma.

Cohort 2: The mean age of the subjects within Cohort 2 (patients with hypertension in 2011 alone) was 62.18±13.92 years, with a gender distribution of 36 males (within cohort - 50.70%) and 35 females (within cohort - 49.30%). The mean BMI was 25.59±5.14 kg/cm^2. Among the 71 subjects in Cohort 2, none of the patients developed either diabetes mellitus or bronchial asthma during the observation period from 2011-2015. The mean time-span for GERD development from the onset of hypertension was 2.33±0.14 years respectively.

Only 12 of the 71 subjects (within cohort - 15.90%) in Cohort 2 developed GERD between the period of observation from 2011-2015. The RR of development of GERD amongst the hypertensives when compared to the overall study population was 1.12, suggesting that the probability of development of GERD amongst hypertensive population is more likely in comparison to the rest of the study subjects. However, a cross-tabulation evaluation of the Cohort 2 population revealed that there was no statistically significant relationship between hypertension and GERD (p=0.748).

Cohort 3: The mean age of the subjects within Cohort 3 (patients with bronchial asthma alone in 2011) was 48.70±17.13 years, with a gender distribution of 23 males (within cohort - 43.40%) and 30 females (within cohort - 56.60%). The mean BMI was 23.26±5.71 kg/cm^2. Among the 53 subjects in Cohort 3, none of the patients developed either diabetes mellitus or hypertension during the observation period from 2011-2015. The mean time-span for GERD development from the onset of hypertension was 6.33±0.56 years respectively.

Only 10 of the 53 subjects (within cohort - 18.90%) in Cohort 3 developed GERD between the period of observation from 2011-

2015. The RR of development of GERD amongst the asthmatics when compared to the overall study population was 1.31, suggesting that the probability of development of GERD amongst asthmatic population is more likely in comparison to the rest of the study subjects. A cross-tabulation evaluation of the Cohort 3 population revealed that there was no statistically significant relationship between bronchial asthma and GERD (p=0.465).

The results of the study have been summarized in [Table/Fig-1]. The values are expressed as frequencies with intra-cohort percentages in parentheses; p<0.05 – statistical significance cut-off.

Further, a binomial logistic regression analysis was performed to account for the impact of the various confounding independent variables like age, sex, body weight and BMI. The results of such an analysis in the overall population as well as separately within each of the three cohorts did not reveal a significant impact of any of these confounding variables on the dependent primary outcome, i.e., GERD development.

Disease Category		GERD n (%)		p-value	Relative Risk	Overall Relative Risk
		Yes	No			
Diabetes Mellitus (DM) n=40	DM alone	2 (5)	25 (62.5)	0.564	0.48	0.56
	DM followed by HTN	0	0	--		
	DM followed by BA	2 (5)	11 (27.5)	0.431	2.01	
	DM followed by HTN followed by BA	0	0	--		
	DM followed by BA followed by HTN	0	0	--		
Hypertension (HTN) n=71	HTN alone	12 (15.90)	59 (84.10)	0.748	1.12	1.12
	HTN followed by DM	0	0	--		
	HTN followed by BA	0	0	--		
	HTN followed by DM followed by BA	0	0	--		
	HTN followed by BA followed by DM	0	0	--		
Bronchial Asthma (BA) n=53	BA alone	10 (18.90)	43 (81.10)	0.465	1.31	1.31
	BA followed by DM	0	0	--		
	BA followed by HTN	0	0	--		
	BA followed by DM followed by HTN	0	0	--		
	BA followed by HTN followed by DM	0	0	--		
Total		**26**	**138**			

[Table/Fig-1]: Summary of the relation between diabetes mellitus, hypertension and bronchial asthma with GERD.

DISCUSSION

The present study was carried out with the aim of investigating diabetes mellitus, hypertension and bronchial asthma as a risk factor for the development of GERD. The present study revealed that the incidence of GERD among the study population was lower than the documented rates in various other studies [2,3,6]. This probably could be attributed to the fact that a better chunk of the studies evaluating the risk of GERD with these diseases have been carried out amongst the Western and Chinese population. An extensive literature search revealed only a few studies that have tried to assess the prevalence of GERD amongst Indian asthmatics [21,22]. The prevalence of GERD noted in these studies was also higher than in the present study. It could be a case of underdiagnoses of GERD within the present study population as this study being retrospective in design did not allow for an objective assessment of GERD using endoscopy or standardized questionnaires, which was the manner of diagnosis of GERD in the two studies within Indian asthmatics [21,22].

The present study suggests that despite the absence of any statistically significant relationship between any of these three diseases and development of GERD, there is a slightly high risk of development of GERD amongst patients with hypertension and bronchial asthma. The lack of statistical significance could be attributed to the inability to meet the pre-decided mark of 130 subjects in each cohort. The findings of our study with respect to asthmatics seem to be in accordance with the results of a recent prospective study conducted amongst Indian asthmatics which concluded that GERD symptoms were more prevalent amongst asthmatics and were closely associated with asthma disease worsening as well [22]. As the present study in its entirety is only focused on investigating whether bronchial asthma can act as a risk factor for GERD, hence a discussion on the worsening of asthma disease course due to GERD is beyond the scope of this manuscript. The theory of increased fluctuations in intra thoracic pressure propelling the acid into the oesophagus asides would appear to have gained a lot of traction in terms of explaining bronchial asthma as a risk factor for GERD development [7]. This could also probably explain the greater risk of GERD amongst diabetic patients within our study who also developed bronchial asthma at some point during the observation period of 2011-2015. However, interestingly, it has also been hypothesized that therapy for asthma using methylxanthines [23,24] and anticholinergics [25] may possibly contribute to the relaxation of the LES, thereby precipitating GERD. An analysis of the asthma medications in the present study revealed that none of the asthma patients received any anticholinergic drugs, though five (9.43% of the total 53 asthmatics) did receive methylxanthine derivatives. It was interesting to note that none of these five patients developed GERD over the course of the observation period from 2011-2015. However, the small sample size does not allow for the deduction of any valid conclusions in terms of whether usage of certain classes of asthma therapeutic agents can act as a risk factor for GERD development.

In case of the hypertensive population, the present study observed a greater risk of developing GERD as compared to the rest of the study population. These findings concur with the results of a cross-

sectional study carried out amongst the Chinese population by Chen T et al. [26] which concluded that hypertension was strongly associated with GERD development. It is well understood that stress and dietary habits along with tobacco and alcohol misuse is associated with high blood pressure [27]. It has been observed that high levels of stress hormones may slow down the gastric emptying [28]. This in turn may allow for an increase in gastric acid and gas production, thereby possibly propelling the gastric contents into the esophagus, culminating in the development of GERD. Though, this hypothesis needs further confirmation, it may possibly explain the increased risk of GERD observed with hypertension. However, these findings are in contradiction to that of another study which suggested that "people who experience daily symptoms of gastro-esophageal reflux have lower blood pressure than people with less frequent or no symptoms" [11]. This inverse relationship was attributed by the authors to an increased level of Nitric Oxide (NO) amongst patients with low or normal blood pressure, which in turn led to a decrease in the LES pressure. Moreover, to support the hypothesis that GERD symptoms may be more prevalent amongst patients with low blood pressure, there exists another line of thought, which states that the lowering of the LES tone by the calcium channel blockers which is a common antihypertensive being prescribed in the Indian population, may possibly precipitate GERD as well [29]. A scrutiny of the antihypertensive medications revealed that of the 71 hypertensive subjects, 37 (52.39%) received oral amlodipine, a calcium channel antagonist. Of these 37, only 8 (21.62%) developed GERD; again, the small sample size precluding us from drawing any conclusion over whether anti-hypertensive therapy with calcium channel antagonists may precipitate GERD.

Curiously though, diabetes mellitus, which has been previously studied extensively and reported as a likely risk factor for GERD, was not observed to pose a risk for GERD development within the present study population. This is in complete contrast to the findings of a meta-analysis which on investigating a relationship between GERD and diabetes mellitus, observed a greater risk of GERD among diabetics [30]. This finding within our study seems to go against the popular perception that diabetic neuropathy may produce motor dysfunction and gastric dysmotility as well as increased incidence of LES distension [31]. However, our study finds support from a recently published case control study carried out by Ha JO et al. [32] which suggested that there was no significant difference between the prevalence of GERD among type 2 diabetics and non diabetics. The authors of the case-control study mentioned here suggest that their results could probably be due to an overestimation of GERD prevalence due to certain logistical issues with respect to the methodology of the study. With respect to the present study, it must be remembered that the final patient sample size in each cohort fell way short of the intended mark of 130 patients due to time constraints and the limitations imposed by the inclusion and exclusion criteria. This could have seriously undermined the predictive power of our study and it would be advisable to exercise caution while drawing conclusions.

CONCLUSION

This study showed the incidence of GERD was lower within the study population compared to other studies carried out in Western and Chinese populations. However, despite the absence of any statistically significant relationship, the risk for GERD development is higher amongst hypertensive and asthmatic patients. The present study did not find any increased risk of GERD amongst diabetics. Furthermore, there is a need for elucidation of the potential underlying mechanisms to provide us with better insights into the manner of development of GERD with these diseases as risk factors.

PROFORMA (Appendix – 1)

Enrolment No.:

Hospital No. :

Age:

Sex:

Address:

Contact No. :

Occupation:

Height:

Weight:

BMI:

Year	Disease	Duration	Treatment
2011	Diabetes mellitus	Y / N	
	Hypertension	Y / N	
	Bronchial Asthma	Y / N	
Others (specify)			
2015	Diabetes mellitus	Y / N	
	Hypertension	Y / N	
	Bronchial Asthma	Y / N	
Others (specify)			

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of Manipal University in allowing the use of their premises and facilities to conduct this study.

REFERENCES

[1] Sun H, Yi L, Wu P, Li Y, Luo B, Xu S. Prevalence of gastroesophageal reflux disease in type II diabetes mellitus. Gastroenterology Research and Practice. 2014;2014:601571.
[2] Wang X, Pitchumoni CS, Chandrarana K, Shah N. Increased prevalence of symptoms of gastroesophageal reflux diseases in type 2 diabetics with neuropathy. World J Gastroenterol. 2008;14;709-12.
[3] Gudlaugsdottir S, Verschuren W, Dees J, Stijnen T, Wilson J. Hypertension is frequently present in patients with reflux esophagitis or Barrett's esophagus but not in those with non-ulcer dyspepsia. Eur J Intern Med. 2002;13(6):369-75.
[4] Moraes-Filho JPP, Navarro-Rodriguez T, Eisig JN, Barbuti RC, Chinzon D, Quigley EMM. Comorbidities are frequent in patients with gastroesophageal reflux disease in a tertiary health care hospital. Clinics (Sao Paulo, Brazil). 2009;64(8):785-90.
[5] Perrin-Fayolle M, Bel A, Kofman J, Harf R, Montagnon B, Pacheco Y, et al. Asthma and gastro-esophageal reflux. Results of a survey over 150 cases (author's transl). Le Poumonet le Coeur. 1980;36(4):225-30.
[6] Sontag SJ, O'Connell SA, Miller T, Bernsen M, Seidel J. Asthmatics have more nocturnal gasping and reflux symptoms than non-asthmatics, and they are related to night-time eating. The American Journal of Gastroenterology. 2004;789–96.
[7] Mittal RK, Balaban DH. The esophagogastric junction. N Engl J Med. 1997;336:924–32.
[8] Lee SD, Keum B, Chun HJ, Bak YT. Gastroesophageal reflux disease in type II diabetes mellitus with or without peripheral neuropathy. Journal of Neurogastroenterology and Motility. 2011;17:274–78.
[9] Horikawa A, Ishii-Nozawa R, Ohguro M, Takagi S, Ohtuji M, Yamada M, et al. Prevalence of GORD (gastro-oesophageal reflux disease) in type 2 diabetes and a comparison of clinical profiles between diabetic patients with and without GORD. Diabet Med. 2009;26(3):228-33.
[10] Ariizumi K, Koike T, Ohara S, Inomata Y, Abe Y, Iijima K, et al. Incidence of reflux esophagitis and H pylori infection in diabetic patients. World J Gastroenterol. 2008;14(20):3212-17.
[11] Murray LJ, McCarron P, McCorry RB, Anderson LA, Lane AJ, Johnston BT, et al. Inverse association between gastroesophageal reflux and blood pressure: results of a large community based study. BMC Gastroenterol. 2008;8:10.
[12] Mastronarde JG. Is there a relationship between GERD and asthma? Gastroenterology & Hepatology. 2012;8(6):401-03.
[13] Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. The Australasian Medical Journal. 2014;7(1):45-48.
[14] World Health Organization (WHO). Noncommunicable diseases country profiles 2011. Available from: http://www.who.int/nmh/countries/ind_en.pdf. [Accessed 20th November 2016].
[15] Kant S. Socio-economic dynamics of asthma. Indian J Med Res. 2013;138:446-48.
[16] Bhatia SJ, Reddy DN, Ghoshal UC, Jayanthi V, Abraham P, Choudhuri G, et al. ISG task force report: epidemiology and symptom profile of gastroesophageal reflux in the Indian population: report of the Indian Society of Gastroenterology Task Force. Indian J Gastroenterol. 2011;30(3):118-27.
[17] World Health Organization/International Diabetes Federation (WHO/IDF). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia.

Available from: http://apps.who.int/iris/bitstream/10665/43588/1/9241594934_eng.pdf. [Accessed 20th November 2016].
[18] American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2010;33(Suppl 1):S62-S69.
[19] World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. Journal of Hypertension. 2003;21:1983-92.
[20] Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Revised 2014. Available from: www.ginasthma.org. [Accessed 20th November 2016].
[21] Sandur V, Murugesh M, Banait V, Rathi PM, Bhatia SJ, Joshi JM, et al. Prevalence of gastroesophageal reflux disease in patients with difficult to control asthma and effect of proton pump inhibitor therapy on asthma symptoms, reflux symptoms, pulmonary function and requirement for asthma medications. J Postgrad Med. 2014;60:282–86.
[22] Gaude GS, Hattiholi J, Bhoma G, Hajare S. Risk of gastro-esophageal reflux disease in bronchial asthma-a prospective study using FSSG scale and gastroesophageal endoscopy. Arch Med. 2016;8:3.
[23] Harding SM. GERD and airway disease. In: Stein MR, ed. Gastroesophageal Reflux Disease. Lung Biology in Health Disease, vol. 129. New York: Marcel Dekker, 1999:139–171.
[24] Ekström T, Tibbling L. Influence of theophylline on gastro-oesophageal reflux and asthma. European Journal of Clinical Pharmacology. 1988;35:353–56.
[25] Lagergren J, Bergström R, Adami HO, Nyrén O. Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. Ann Intern Med. 2000;133(3):165-75.
[26] Chen T, Lu M, Wang X, Yang Y, Zhang J, Jin L, et al. Prevalence and risk factors of gastroesophageal reflux symptoms in a Chinese retiree cohort. BMC Gastroenterol. 2012;12:161.
[27] American Heart Association/American Stroke Association (AHA/ASA). Understanding and Managing High Blood Pressure. Available from: https://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_461840.pdf. [Accessed 20th November 2016].
[28] Gué M, Peeters T, Depoortere I, Vantrappen G, Buéno L. Stress-induced changes in gastric emptying, postprandial motility, and plasma gut hormone levels in dogs. Gastroenterology. 1989;97(5):1101-07.
[29] Hongo M, Traube M, McAllister RG Jr, McCallum RW. Effects of nifedipine on esophageal motor function in humans: correlation with plasma nifedipine concentration. Gastroenterology. 1984;86:8-12.
[30] Sun X-M, Tan J-C, Zhu Y, Lin L. Association between diabetes mellitus and gastroesophageal reflux disease: a meta-analysis. World J Gastroenterol. 2015;21(10):3085-92.
[31] Shakil A, Church RJ, Rao SS. Gastrointestinal complications of diabetes. Am Fam Physician. 2008;77(12):1697-702.
[32] Ha JO, Lee TH, Lee CW, Park JY, Choi SH, Park HS, et al. Prevalence and risk factors of gastroesophageal reflux disease in patients with type 2 diabetes mellitus. Diabetes Metab J. 2016;40(4):297-307.

PARTICULARS OF CONTRIBUTORS:
1. Undergraduate Student, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.
2. Undergraduate Student, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.
3. Associate Professor, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.
4. Postgraduate Candidate, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Bharti Chogtu,
Associate Professor, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal-576104, Karnataka, India.
E-mail: bhartimagazine@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Nov 22, 2016**
Date of Peer Review: **Jan 14, 2017**
Date of Acceptance: **Jun 07, 2017**
Date of Publishing: **Jul 01, 2017**