Original Article

Dietary Nitrate may have A Role in Development of Gastro-Esophageal Reflux Disease

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Abstract

Background: Gastro-esophageal reflux disease (GERD) has become very common in the past three decades. The reason for this, as well as its exact pathophysiologic mechanisms are yet unknown. In this ecologic study we assessed the relation between water nitrate content and prevalence of GERD in Tehran, Iran.

Methods: We determined the prevalence of acid regurgitation (AR) heartburn or any of them occurring on a frequent (at least weekly) or infrequent basis in areas with different water nitrate. The areas for nitrate were defined as below: <50mg nitrate/L, 50 – 74 mg/L, 75 – 100 mg/L, and >100 mg/L. Frequency of each symptom was assessed in each area and compared. Adjustment for age, sex, education, NSAID-consumption, BMI, smoking, history of GERD in first degree relatives and spouse was done in a multivariate model.

Results: People living in areas with water nitrate content more than 100mg/L had a higher chance of suffering from frequent AR than those living in areas with water nitrate less than 100mg/L (25.5% vs. 12.0%, OR: 2.53, 95% CI: 1.36 – 4.73, *P*=0.006). After adjustment for the named factors, the relationship remained significant (OR: 3.65, 95% CI: 1.32 – 10.09). The relation for frequent heartburn or infrequent symptoms was not significant.

Conclusion: In this ecologic study, we found relation between experiencing frequent AR and drinking or cooking with water containing more than 100mg nitrate/L. Considering our current knowledge, if we put dietary nitrate into the puzzle of increased prevalence and/or pathophysiology of GERD, it can theoretically answer several questions. Hence we propose a nitrate-hypothesis for GERD pathogenesis.

Key words: epidemiology, GERD, nitrate, pathogenesis, water

Introduction

Gastro-esophageal reflux disease (GERD) is a common chronic disease, prevalence of which has increased dramatically over the past three decades in different parts of the world.[1–5] This has generated lots of enthusiasm on GERD pathophysiology and the possible underlying mechanisms leading to GERD. Our current knowledge implies that pathologic "transient lower esophageal relaxation, "pt-LESR" stands for many GERD episodes, and that this phenomenon is governed by multiple factors. This mechanism, although rational and practical, leaves lots of unanswered questions. For instance: "why all pt-LESRs are not associated with reflux?", "why all reflux episodes are not associated with pt-LESRs?", "what has contributed to this amount of increase in pt-LESRs in the community over the past three decades?", "why all pt-LESR associated reflux episodes do not cause GERD symptoms?" and many more like these.[6–10] Therefore, there is much more room for research in this field to unravel the main mechanism causing GERD and/or t-LESRs as well as the reason for such increase in GERD burden in many parts of the world.

Ecologic studies, although not able to show cause and effect relationships in most instances, are fascinating and helpful in hypothesis generation. In this ecologic study, which is an extension of a population based study on prevalence of GERD in Tehran, we assessed the relationship between "nitrate content of drinking water" and prevalence of GERD in different provinces of Tehran, the capital of Iran.

Materials and Methods

In a population based study we had assessed the prevalence of GERD in Tehran.[2] Briefly a randomized clustered sample of Tehran province permanent households was selected, and individuals between 18 to 65 years of age were given a validated Persian translation of the Mayo gastro-esophageal reflux questionnaire (GERQ).[11] The GERQ contains detailed questions on major and minor GERD symptoms as well as their frequency and duration. GERD was diagnosed as presence of at least weekly episodes of heartburn and/or acid regurgitation during the last 12 months. In this study over 2,500 individuals were given the GERQ and about 80% returned the completed questionnaires.

Tehran is a metropolitan city with more than 12,000,000 inhabitants. The water supply is made available through large dams and multiple deep wells. Therefore the quality of water may differ in various areas. Data on nitrate content of drinking water for different areas of Tehran was obtained from the regional water organization of Tehran. We categorized regions based on their nitrate level in water; areas with nitrate level less than 50mg/L, areas with nitrate level between 50 and 75mg/L, areas with nitrate level between 75 and 100 mg/L and areas with nitrate level more than 100 mg/L. Then, we studied the prevalence of GERD in different regions according to their water nitrate content. Frequent (at least weekly) heart burn (HB), frequent acid regurgitation (AR), frequent GERD (either HB or AR), infrequent (less than once a week) heart burn,

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infrequent acid regurgitation and infrequent GERD in various areas were assessed. Odds ratios and 95% confidence intervals (CI) were calculated. Then, we adjusted associations for sex, age, education level, smoking, BMI, NSAID consumption, positive history of GERD in first degree relatives and positive history of GERD in spouse in a multivariable regression model.

Results

Of the 2,561 eligible subjects (42.3% men, response rate: 84.8%) 2,058 (80.4%) were included in the final analysis. The prevalence of frequent AR, infrequent AR, frequent HB and infrequent HB were 15.7%, 25.5%, 10.7%, and 11.8%, respectively.

Nitrate levels in drinking water were as follow: 20.0% areas with nitrate level under 50mg/L, 62.1% areas with nitrate level between 50 and 75mg/L, 15.0% areas with nitrate level between 75mg/L and100mg/L and 2.9% areas with nitrate level more than 100mg/L. Individuals living in areas with drinking water containing more than 100mg/L nitrate were more likely to experience frequent AR than people who lived in areas with water containing less than 100mg/L nitrate (25.5% vs. 12.0%, OR: 2.53, 95%CI: 1.36 – 4.73, *P*=0.006). After adjustment for sex, age, education level, smoking, BMI, NSAID consumption, positive family history for GERD and positive spouse history for GERD, the correlation remained significant. We repeated this analysis for infrequent AR, frequent HB and infrequent HB but we did not find any significant correlation (Table 1). The chances of experiencing infrequent AR was higher in areas with water nitrate less than 50mg/L than those with more than 50mg/L (Table 1).

Discussion

Increasing GERD prevalence in different populations has been attributed to various factors, but so far no truly causative agent(s) has been identified. Hence, the cause of this new epidemic is yet unknown. Recent data has shown that high nitrates in association with Ascorbic acid can induce serious esophageal damage in mice with mechanical reflux, while reflux induction alone cannot do so.[12] Another recent study has shown that nitrates can induce dilated intercellular space in the esophagus.[13] In addition, nitrate and nitrite have been increasingly used for cultivation of edible plants and roots as well as in food industry as a preservative. Our data shows that drinking or making food using water with nitrate levels more than 100mg/L regularly, correlates with experiencing frequent (at least weekly) acid regurgitation. We believe this outcome from a comprehensive ecologic study endorses the hypothesis of nitrate's contributing role in GERD occurrence through the following pathway: dietary nitrate is absorbed in the stomach and proximal small intestine and is secreted again in the saliva through an efficient entero-salivary circulation.[14,15] The secreted nitrate in the salivary glands is reduced to nitrite by bacteria residing on the dorsum of the tongue.[11] The nitrite produced in this way comes in contact with gastric acid and ascorbic acid at the gastro-esophageal junction and abundant nitric oxide (NO) is produced.[16,17] NO diffuses across the mucosa and gives rise to active metabolites on the other side of the mucosal surface.[18–20] In addition, it can mediate relaxation of the lower esophageal sphincter, increased t-LESR and sensitization of the mucosa to the regurgitated gastric contents.[21–23,11] This concept can also explain the inverse association of HP infection with GERD. In patients infected with HP, gastric acid secretion as well as gastric ascorbic acid secretion is decreased. This sets off the above mentioned mechanism. With HP elimination, gastric acidity and gastric ascorbic acid production reach levels which potentiate the above-mentioned pathway leading to increased gastro-esophageal reflux.[3,18] Nitric oxide produced at the gastro-esophageal junction may also sensitize the lower esophagus to gastric content regurgitation through dilated intercellular space. Hence this so-called "nitrate hypothesis" for GERD may also be

Table 1. Frequency of acid regurgitation (AR), heartburn (HB), and GERD (either AR or HB) in different areas in Tehran according to drinking water nitrate.

Water / Nitrate clinical findings	<50 mg/dL	51 – 75 mg/dL	76 – 100 mg/dL	>100 mg/dL	<50 vs. >50		<75 vs. >75		<100 vs. >100		<50 vs. >100	
					OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Frequent* HB	9.9%	10.0%	7.2%	12.7%	0.92 (0.64 – 1.31)	0.64	0.79 (0.52-1.21)	0.31	1.37 (0.61 – 3.09)	0.48	1.33 (0.56 – 3.15)	0.48
Infrequent* HB	11.2%	10.6%	8.6%	14.5%	0.96 (0.66 – 1.41)	0.84	0.87 (0.59-1.30)	0.56	1.46 (0.68 – 3.14)	0.36	1.35 (0.60 – 3.05)	0.49
Frequent AR	12.2%	11.7%	12.1%	25.5%	1.00 (0.71 – 1.41)	1.00	1.23 (0.88-1.73)	0.23	2.53 (1.36 – 4.73)	0.006*	2.45 (1.24 – 4.84)	0.01*
Infrequent AR	26.5%	22.6%	16.6%	12.7%	0.74 (0.57 – 0.96)	0.02*	0.61 (0.45-0.83)	0.002*	0.50 (0.22 – 1.11)	0.10	0.47 (0.20 – 1.11)	0.10
Frequent GERD	17.4%	18.7%	15.9%	27.3%	1.07 (0.80 – 1.44)	0.65	0.95 (0.70-1.29)	0.81	1.70 (0.93-3.12)	0.10	1.78 (0.93– 3.40)	0.09
Infrequent GERD	28.5%	24.1%	17.6%	16.4%	0.73 (0.56 – 0.94)	0.01*	0.62 (0.46-0.87)	0.002*	0.62 (0.30 – 1.27)	0.25	0.50 (0.23– 1.07)	0.09

*= Frequent=at least weekly occurrence, Infrequent=less than weekly occurrence.

able to answer other formerly mentioned questions. For instance, if adequate NO is produced with availability of enough nitrite, then regurgitation of gastric contents lead to symptoms, while gastric content regurgitation in the absence of adequate nitrite and ascorbic acid does not so.

In conclusion, we have shown that high nitrate content of drinking water is associated with frequent acid regurgitation among inhabitants of Tehran. We hypothesize that increased dietary nitrate may have a pivotal role in development of the GERD epidemic currently encountered in many parts of the world, especially the more affluent parts. This is in accord with recent animal findings regarding GERD development. If this is verified in further well-designed studies, we may be able to approach GERD in a totally different way than we do now and it may have significant impact on patients' outcomes and therapeutic approach.

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