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RESEARCH ARTICLE

Analysis of Probable Risk Factors of Gastric Intestinal Metaplasia in Patients Referred to the Gastroenterology Clinic with Dyspepsia

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Abstract

Background: Gastric intestinal metaplasia is known as a precursor of gastric cancer in the cascade of events from chronic gastritis to gastric adenocarcinoma. Given the risk of developing gastric cancer in patients with gastric intestinal metaplasia, periodic screening of these lesions for early detection of malignant transformation seems logical. Risk factors of these lesions are worth to be searched and modified due to prevalence and mortality rate of gastric cancer in Iranian population. **Material and methods:** In this case-control study, 39 patients with and 39 patients without intestinal metaplasia who were attended to the gastroenterology clinic from 2017 to 2021 for upper gastrointestinal endoscopy due to dyspepsia were enrolled. Probable risk factors of gastric intestinal metaplasia were compared between two mentioned groups. **Results:** According to the presented study, there was a significant link between Turk race (P-value=0.014), couples (p-value=0.033), smoking (p-value=0.009), cholecystectomy (p-value=0.033), active helicobacter pylori infection (p-value=0.018) and prevalence of gastric intestinal metaplasia. There was also a significant association between consumption of fast food (p-value=0.037) as well as proton-pump-inhibitors (p=value=0.028) and risk of gastric intestinal metaplasia. Blood group A was also statistically related (p-value=0.012) to the gastric intestinal metaplasia. **Conclusion:** According to the results, the chance of metaplasia in Turk race, married people, blood group A, people with history of smoking, active helicobacter pylori infection and history of cholecystectomy is shown to be more than other people. Detrimental diets including fast food as well as consumption of proton-pump-inhibitors were detected to be related to gastric intestinal metaplasia. To corroborate the results, the small sample size of the presented study should be supplemented by more studies with more participants.

Keywords: Gastric cancer- Intestinal metaplasia- *H. pylori* infection

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Introduction

Gastric cancer as a common cancer worldwide with a low five-year survival [1] is not diagnosed at early stages due to the lack of symptoms. Missed diagnosis at early stages in addition to invasive characteristic of disease itself result in rapid progression of cancer to the end stages of the disease and death [2]. This cancer might be cured if found at initial stages [3]. Approximately, gastric cancer is assigned 14% of all malignancies in men to itself. It is reported that gastric cancer is the most common malignancy in men and the third most common cancer in women. It is also known as the most common cause of cancer related death in Iran [4]. Global statistics also confirm prevalence of gastric cancer as the first and third malignancy in men and women, respectively [5]. It is

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common in the sixth decade of life, although it has also been detected earlier. This malignancy requires a prompt diagnosis and treatment [6]. Having written about the burden of gastric cancer, the paramount issues are whether we can blame pre-malignant lesions for creating gastric cancer or not, whether we can detect and ablate these lesions before they become malignant or not, and more essential to address if we can detect and omit the culprit risk factors or not? The focus of the present study is to evaluate presence of some of the proposed risk factors for gastric intestinal metaplasia (GIM) in patients referred to the gastroenterology clinic of Taleghani hospital with dyspepsia. As it is the case, GIM is a key step in the Correa cascade [7] in the pathogenesis of gastric cancer. In this pathway, chronic mucosal inflammation with mixture of polymorphonuclear and mononuclear cells is substituted by scattered or diffuse atrophy of gastric glands and parietal cells leading to formation of metaplastic intestinal epithelium comprising goblet cells. Eventually, dysplastic cells with neoplastic contents (so-called early mucosal cancer) are substituted for gastric atrophy [7]. Triggering etiologies in this cascade are *H. pylori* infection, autoimmune reaction, Epstein-Barr virus (EBV), smoking, high salt intake, and nitrous compounds. When it comes to classification of GIM, histologic evaluation and endoscopic extension of the involved region are of great importance for risk-stratification of the intestinal metaplasia. Histologically complete GIM which is small intestinal type containing goblet cells and brush border is detected at early stages in contrast to the incomplete GIM which is large intestinal type without brush border and without regular goblet cells found in advanced stages [8]. Histologically operative link on gastritis assessment (OLGA) classification is used to assess the extension of gastric atrophy and intestinal metaplasia. With this regard, stage III and IV of OLGA classification represent severe extension of gastric atrophy or GIM and strong probability of transformation to dysplasia and cancer. Stage III and IV of OLGA classification are considered for patients with severe atrophy of antrum and incisura angularis regardless of presence of corpus atrophy as well as patients with moderate or severe atrophy of corpus following at least moderate atrophy of antrum and incisura angularis. GIM in patients with high-risk variables suggestive of progression of disease including incomplete GIM, OLGA III or IV, history of gastric cancer in first degree relatives, and residents or immigrants of areas with high prevalence of gastric cancer is considered for triennial endoscopic surveillance [9]. To evaluate OLGA classification, gastric topographic biopsy mapping is required. Resultantly, patients with GIM in a random biopsy from stomach are advised to repeat endoscopy with targeted and nontargeted biopsies in 1 year. Intestinal metaplasia is a contributing factor of gastric cancer [10,11] requiring an intermittent screening for gastric cancer [12]. Gastric carcinoma would be detected at the location of intestinal metaplasia. Since gastric cancer is related to the severity and extension of intestinal metaplasia, recognition of risk factors of intestinal metaplasia as well as early diagnosis and optimal follow-up of patients with intestinal metaplasia may be a good approach to reduce the mortality and imposed burden of gastric cancer [13-16]. The pattern of prevalence of gastric cancer shows a high prevalence of gastric cancer in rural areas, Asia, and Iran in contrast to the other parts of the western societies. This is might be due to the geographical, racial and environmental factors [4]. In the present study, we have attempted to evaluate the risk factors of intestinal metaplasia in patients referred to gastroenterology clinic of Taleghani hospital, a tertiary center in Tehran, Iran with dyspepsia from 2017 to 2021.

Materials and Methods

This is a case-control study on 78 consecutive patients attending to gastroenterology clinic from 2017 to 2021 including 39 patients with and 39 subjects without intestinal metaplasia according to the pathologic reports of gastric endoscopic samples. Patients with reported complete or incomplete GIM (OLGA I, II, III and IV) who were older than 18 after a written informed consent regardless of status of *H. pylori* infection were included in the study and were sent to the case group. Patients with reported GIM but without gastric topographic mapping biopsy were sent for re-endoscopy and standard mapping biopsy and then entered the study. Due to the prevalence of *H. pylori* infection in the area, all of the patients in the case group were advised to receive *H. pylori* eradication regimen and check for *H. pylori* eradication in an appropriate time after cessation of drugs. Additionally, patients in the case group were suggested to have a surveillance endoscopy in 3 years due to the fact that gastric cancer is still rising in our country despite its global downward trend. Patients older than 18 with dyspepsia and endoscopic random biopsies negative for GIM (OLGA 0) were sent to the control arm. Patients younger than 18, patients with previous personal history of gastric cancer, previously treated for *H. pylori* infection, belonging to the genetic syndromes which increase the probability of gastric cancer, patients without gastric topographic mapping, and patients not assigning the written informed consent were excluded from study. Biopsies were taken from at least six zones of stomach including lesser curvature of body and antrum, greater curvature of body and antrum, and incisura angularis. The study was approved by the ethical code of IR.SBMU.MSP.REC.1397.227 in ethic committee approval of Shahid Beheshti University of Medical Sciences, Tehran, Iran. Studied variables were age, ethnicity, marital status, job, literacy, smoking, alcohol use, substance use, previous medical history, poor dietary habits, past drug history, blood group, and anthropometric measurements. The referred patients to the center were all Iranians but from different ethnicities including Turks (Turkish race constitutes the largest minority in Iran commonly living in Iranian Azerbaijan although they also live scattered all over Iran. Their first language is Turkish.), Farses or Persians (They are the largest group of Iranians. Their first language is Persian. They live in major cities of Iran including Tehran, Isfahan, Fars,… as well as smaller cities), and Arabs (They are the Arab inhabitants of Iran,

commonly living in Khuzestan. Their mother language is Arabic.) Poor dietary habits were assessed using questionnaires that evaluated frequency of consumption of food which are low in nutrients including vitamins, minerals, and fiber and high in calory, saturated fat, refined sugar, salt, and preservatives. Resultantly, consumption of fast food which is high in fat and carbohydrates, consumption of pickles which are high in sodium due to process of brining, eating food with preservatives, and adding salt to food after cooking were assessed during the last 3 years. High-school certificate was considered as cutoff for having academic literacy. Former smokers (≥100 cigarettes in lifetime) and current smokers, both were considered smoker in this study. In terms of alcohol consumption, alcohol intake more than 7 drinks per week for women and more than 14 drinks per week for men was considered significant. in this study. In the present study, substance abuse is defined as usage of illicit drugs including opium, amphetamines, etc. excluding cigarette and alcohol. In terms of anthropometric measurements, BMI of participants was evaluated and compared between cases and controls. Past medical and past surgical history of participants were collected for Cholecystectomy, gastrointestinal and non-gastrointestinal malignancies, autoimmune diseases, diabetes mellitus, hypertension, renal disease, and *H. pylori* infection. All the mentioned variables were compared across the groups.

Statistical analysis

Data analysis was performed by IBM SPSS version 24.0, Chicago, IL. Mean and standard deviations were assessed for numerical variables. Frequency and percentage were determined for categorical variables. Chi-square (for frequencies ≥ 5) and fissure exact tests (for frequencies less than 5) were used to determine whether or not there is a significant association between categorical variables with a significance level of 0.05 and confidence interval of 95%.

Results

Demographic analysis of patients revealed that population's characteristics were not significantly different between two groups of present study except for race. As we can see in Table 1, mean age of total participants was 51.2 ± 13.7 ranging from 21-84 years without significant difference (49.9 ± 13.6 for controls versus 52.5 ± 13.9 for cases, P=0.417). 30.8% and 43.6% of participants were male in cases and controls, respectively without significant difference (P=0.24). The percentage of married participants was 92.3% for cases vs 74.4% for controls which was statistically different between two groups (P=0.033). Races were Fars, Turk, and Arab in 56.4%, 25.6%, and 18%, respectively in control group and 25.6%, 53.8%, and 20.5%, respectively in case group showing significant difference (P=0.014). Farses were significantly dominant in patients without GIM and Turks were dominant in case group. Academic literacy was found in 19 and 18 subjects of control and case groups, respectively without significant difference (P=0.821). Employment status as well as academic literacy was not found to be related to the GIM in this study (P=0.368). The mean BMI was 24.96 ± 3.4 and 28.95 ± 2.3 kg/m² in controls and cases, respectively without significant difference (P=0.276). History of illicit drug use between two groups was not meaningfully different except for smoking. As can be driven from Table 2, a total of 38.5% and 12.8% of controls and cases were smokers (P=0.009), 20.5% and 10.25% of controls and cases were alcohol users (P=0.074), and only one patient in each group was substance user (P=1.000). Alcohol intake more than 7 drinks per week for women and more than 14 drinks per week for men was considered significant. Given the past medical history of participants in Table 3, a significant difference

Table 1. Demographic Characteristics

Demographic characteristic	Control (n=39)	Case (n=39)	P-value
Sex			
Female n (%)	22 (56.4)	27 (69.2)	0.24
Male n (%)	17 (43.6)	12 (30.8)	
Age Mean (±SD)	49.9 (± 13.6)	52.5 (± 13.9)	0.417
BMI Mean (±SD)	24.96 (± 3.4)	28.95 (± 2.3)	0.276
Marital status			
Married n (%)	29 (74.4)	36 (92.3)	0.033
Single n (%)	10 (25.6)	3 (7.7)	
Academic literacy n (%)	19 (48.72)	18 (46.15)	0.821
Employment status			
Employees n (%)	15 (25.6)	13 (7.7)	0.368
Unemployed n (%)	24 (48.72)	26 (46.15)	
Races			
Fars	22 (56.4)	10 (25.6)	0.014
Turk	10 (25.6)	21 (53.8)	
Arab	7 (18)	8 (20.5)	

Table 2. History of Illicit Drugs

History of illicit drugs	Control (n=39)	Case (n=39)	P-value
Smoking n (%)	5 (12.8)	15 (38.5)	0.009
Alcohol use n (%)	8 (20.5)	4 (10.25)	0.21
Substance use n (%)	1 (2.6)	1 (2.6)	1

Table 3. Past Medical History and H. pylori Status

Past medical history	Control (n=39)	Case (n=39)	P-value
Cholecystectomy n (%)	3 (7.7)	10 (25.6)	0.033
Malignancy			
Gastrointestinal n (%)	0 (0)	2 (5.13)	0.891
Non-gastrointestinal n (%)	0 (0)	3 (7.7)	
Autoimmune diseases n (%)	7 (17.9)	11 (28.2)	0.28
Diabetes mellitus n (%)	8 (20.5)	9 (23.07)	0.783
Hypertension n (%)	7 (17.9)	8 (20.5)	0.773
Renal diseases n (%)	4 (10.2)	2 (5.13)	0.395
H. pylori infection n (%)	9 (23.07)	19 (48.72)	0.018

was found in history of cholecystectomy between cases and controls. 3 of controls and 10 of cases had previous cholecystectomy (P=0.033). History of malignancy was reported in 12.8% of cases (2 gastrointestinal and 3 non-gastrointestinal) versus none of the participants of control group (P=0.891). History of autoimmune diseases was positive for 18 members including 2 cases of rheumatoid arthritis (RA) and 5 cases of lupus in control group and 1 case of lupus and 10 cases of RA in case group (P=0.28). Active *H. Pylori* infection was seen in 9 participants of control group and 19 participants of case group. As could be seen in Table 3, active *H. pylori* infection was significantly associated with GIM (P=0.018). There was no meaningful difference between cases and controls for diabetes mellitus (P=0.314), hypertension (P=0.555) and renal disorders (P=0.247). Comparison of percentage of participants who had poor dietary habits among cases and controls revealed that unhealthy diet might be an indicator of the probability of GIM especially following with high fast-food intake. As shown in Table 4, consumption of fast food was statistically higher in case group (P=0.037). Statistics did not show any difference for consumption of salt (p-value=0.081), pickles (P=0.751) and preservatives (P=0.078). As reflected in Table 5, percentage of variety of blood groups in cases and controls was significantly different (P=0.015). Accordingly, A+ was the most common blood group among patients with GIM. Evaluation of past drug history of participants via chi-square test of independence determined that there is an association between consumption of PPI and presence of GIM (P=0.016). The results are shown in Table 6. The serum level of micronutrients was measured for zinc, vitamin B, and vitamin D which were normal for 19, 37, and 19 participants of control group and 17, 30, and 23 members of case group, respectively without any difference (P > 0.05).

Discussion

GIM is a known risk factor of gastric cancer and detection of modifiable risk factors for GIM can help decrease the number of gastric cancers related to. As could be driven from the results, mean age of participants totally was 51.22 ± 13.7 years and there was not any significant difference between mean age of cases and controls. Majority of subjects in both groups of cases and controls were female, but this dominancy was not statistically significant. These results are in contrast to the studies that introduce male gender and old age as important factors of GIM [17,18]. This discrepancy needs more studies with larger sample sizes to be corroborated. *H. pylori* infection is known to be a major risk factor of gastric intestinal metaplasia as seen in the present study, too [19]. A large study on 28745 patients since 2008 to 2013 revealed a significant association between intestinal metaplasia and *H. Pylori* infection [20]. Intestinal metaplasia recognition as well as gastric cancer is seen in low proportion of patients with *H. Pylori* infection. It shows the probability of other environmental and genetic factors involved in presence and progression of metaplasia into the gastric cancer [20,21]. Generally, chronic active gastritis is the result *H. pylori* infection in all patients with active *H. pylori* infection. Of them, only about 10% progress to severe atrophic gastritis [22]. Male gender, positive history for gastric cancer in first-degree relatives, old age, patient's polymorphism for IL1B, and genotype Vac A of *H. pylori* are also known as contributing factors in progression of *H. pylori* infection and chronic active gastritis to gastric cancer [23-25]. Association between smoking and intestinal metaplasia has been assessed in different studies and an increased risk of gastric cancer has been confirmed among smokers [26]. The results for association of smoking and GIM are somehow controversial since it is not clear if detrimental effects of cigarette smoking is due to progression of GIM to neoplastic tissue or formation of GIM itself. In the present

Table 4. History of Dietary Pattern and Food Habits

Past medical history	Control (n=39)	Case (n=39)	P-value
Fast food n (%)			
No consumption	13 (33.33)	5 (5.13)	0.037
Monthly or less	22 (56.41)	21 (53.84)	
Weekly	4 (10.26)	11 (28.20)	
Daily	0 (0)	2 (5.13)	
Food with preservatives n (%)			
No consumption	12 (30.77)	15 (38.5)	0.078
Monthly or less	23 (58.97)	14 (35.9)	
Weekly	4 (10.26)	10 (25.6)	
Daily	0 (%)	0 (%)	
Pickles n (%)			
No consumption	7 (17.9)	11 (28.2)	0.751
Monthly or less	18 (46.15)	15 (38.5)	
Weekly	11 (28.21)	10 (25.6)	
Daily	3 (7.7)	3 (7.7)	
Salt n (%)			
Without salt	7 (17.9)	0 (0)	0.081
Salt consumption only during cooking	20 (51.3)	25 (64.1)	
Salt consumption during cooking and eating	12 (30.77)	14 (35.9)	

Table 5. Variety of Blood Groups among Participants

Variety of blood groups		Control (n=39)	Case (n=39)	P-value
A	Rh+ n (%)	5 (56.4)	16 (69.2)	0.012
	Rh- n (%)	3 (43.6)	3 (30.8)	
B	Rh+ n (%)	4 (%)	4 (%)	
	Rh- n (%)	1 (%)	0 (%)	
AB	Rh+ n (%)	4 (%)	1 (%)	
	Rh- n (%)	7 (%)	1 (%)	
O	Rh+ n (%)	11 (%)	14 (%)	
	Rh- n (%)	4 (%)	0 (%)	

study, a significant association was found between smoking and GIM. Studies are also emphasizing on the current smokers or former smokers with quitting smoking for no more than 15 years [27]. Current smokers and former smokers had not been separated in the present study necessitating more studies in this group of patients with special attention to the nuances of the time and amount of smoking. The mentioned association was not found for other illicit drugs in this study. A chi-square of independence revealed significant association between some poor nutritional habits and GIM. Fast food consumption is shown to be significantly related to intestinal metaplasia in the present study. This is in line with study of Tan et al that shows a strong relation between high-calory/high-carbohydrate diet and GIM [28]. This association was not found for pickles, high salt diet and processed food. Study of Taborda et al also shows that high consumption of food and vegetables can decrease the risk of GIM. Same as the results of our study, survey of Taborda et al did not find any effect for high-salt intake in contrast to the majority of studies in the literature that introduce high salt intake as triggering factor for GIM. These conflicting results need more attention and evaluations [29]. The study of Oh et al [30] on 448 first-degree relatives of patients with gastrointestinal cancers similarly reported a significant difference in consumption of high salt intake and GIM (P=0.047, OR=1.52). Per the revised literature, contradictory results are obtained for the role of salt intake, unhealthy food, low intake of fruits and vegetables in intestinal metaplasia [30-32]. Further studies are required to approve a special regimen for prevention of gastric intestinal metaplasia at least for high-risk patients. Inappropriate dietary habits, use of fast food, coffee, low physical activity and sleep disorders would result in peptic ulcer disease, intestinal metaplasia, and gastric cancer [19,33-35]. Based on chi-square of independence, current study shows that metaplasia probability was not related to employment status of participants, but there are large number of different studies that show gastric cancer is related to low socioeconomic status maybe due to exposure to the poor dietary habit and harmful environmental contacts. In this regard, high percentage of

Table 6. Past Drug History

Past drug history	Control (n=39)	Case (n=39)	P-value
PPIs n (%)	10 (25.6)	23 (58.97)	0.028
H2 blockers n (%)	5 (12.82)	5 (12.82)	1
NSAIDs n (%)	1 (2.6)	0 (0)	0.5

gastric intestinal metaplasia in farmers is indicative of association between gastric intestinal metaplasia and soil nitrate, food preservation without refrigerator, and lack of health facilities in rural regions [36]. Studies evaluating the relation between racial/ethnic diversity and GIM are not rich. Study of Nguyen et al shows that Hispanic and African-Americans in the USA are more prone to the GIM in comparison with other races in the USA [37]. Our study showed a higher trend for GIM in Turkish participants. The results attributed to the race and ethnicity should be interpreted with caution due to the presence of a large number of confounding factors including the effect of immigration, special dietary habit in each ethnicity, different prevalence of *H. pylori* infection in various ethnicities, different health infrastructures for different ethnicities, etc. So, the results are not only due to different genetic background of each ethnicity. Study of Ayvaz et al shows higher incidence of GIM in Afghans than Turkish population [38]. Study of Olmez et al on Turkish population revealed that gastric cancer is a health problem in Van. The prevalence of GIM and associated risk factors were evaluated in this study. *H. pylori* infection in this group of patients was known as a contributing factor for prevalence of GIM and gastric cancer in Turkish people living in Van. It is felt that prevalence of GIM in Turkish people should be assessed after adjusting confounding factors like *H. pylori* infection [39]. This study is in contrast with other studies which suggest the proportion of GIM would be lower due to better mental and emotional status of couples [40]. Majority of participants in two groups were married especially in case group. The chi-square test of independence revealed that marital status and being married are significantly related to GIM. Sun et al evaluated the effect of sociodemographic disparities on gastric cancer and GIM. Based on their study, sex and age were introduced as effective variables on prevalence of gastric cancer and GIM in Chinese population. However, they postulated that low socioeconomic status and low educational level can be evaluated as risk factors of neoplastic and preneoplastic lesions [41]. Marital status as a factor related to the socioeconomic and emotional status of participants should be interpreted with caution. The chi-square test of independence showed that there is a strong relationship between chance of metaplasia and history of some diseases. As could be driven from the results, participants with cholecystectomy and history of active *H. pylori* infection are more likely to have GIM. These results are in line with other studies around the world [42,43]. Cholecystectomy is known as risk factor for some gastrointestinal cancers including gastric cancer. It may be in part due to excess gastroduodenal reflux after cholecystectomy and changes in gastrointestinal microbiota [44]. One of the limitations of the present study is its small sample size in 2 arms of study which can impact on the effect size and power of study. Further studies with larger sample sizes and in wider geographical areas should be carried out if we wanted to rely on the results and suggest a programmed endoscopic surveillance for patients with non-modifiable risk factors of GIM. Also, long-term interventional studies with focus on the reduction of modifiable risk factors for GIM and gastric cancer should be designed to recommend a strict preventive strategy for patients at risk for gastric cancer and GIM based on the present study as well as first degree relatives of patients with gastric cancer [45]. So, the results should be interpreted with caution since the sample size is small. However, the results would be a valuable clue for further studies.

In conclusion, according to the results, the chance of metaplasia would be more in Turks, couples, participants with history of cholecystectomy, active *H. pylori* infection, consumption of fast food, people with O blood group, consumption of PPIs. As a result, modification of some detrimental diets, early diagnosis and eradication of *H. pylori* infection for people at risk for gastric cancer seems to be logical. Further studies in this field can be a complement to the present study and can help better interpretation of the reported results.

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List of abbreviations

BMI: Body Mass Index, EBV: Epstein-Barr virus, GIM: Gastric Intestinal Metaplasia, H. Pylori: Helicobacter Pylori, OLGA: Operative Link on Gastritis Assessment.

Statements & Declarations

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Competing interests

There was no conflict of interests.

Author contributions

LM, Follow up of the patients, Critical review, Basic concept; MF, Follow up of the patients, Preparing data, Basic concept; NS, Writing the manuscript, Preparing data; SF, Writing the manuscript, Preparing data; PKM, Corresponding author, Writing manuscript, Finial edition

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the ethical code of IR.SBMU.MSP.REC.1397.227 in ethic committee approval of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication.

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