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Original Research Paper

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LABORATORY MARKERS OF GASTRIC INTESTINAL METAPLASIA

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ABSTRACT With increasing number of patients diagnosed with gastric cancer screening is gaining more importance. Risk factors of gastric intestinal metaplasia has been reported as presence of Helicobacter pylori infection, older ages, smoking history, taking spicy food, occupation status and the presence of IL10-592 C/A.

At total; 85 patients were enrolled in the period of May 2018-August 2018, laboratory results and abdominal ultrasound were collected. There were taken gastric biopsies in patients who underwent gastroscopy beause of other reasons. All gastroscopies were performed with Fujinon-Videoscopes (Tokyo, Japan).

Non-alcoholic fatty liver disease (NAFLD) was determined with the abdominal ultrasonography. A possible relationship between NAFLD and intestinal metaplasia was investigated. Using laboratory parameters we could not testify any relation between NAFLD and intestinal metaplasia, regarding Helicobacter pylori-status, lipid-and diabetes parameters. Significant differences were found in patients with intestinal metaplasia in terms of lower ferritin and higher TSH values.

Perhaps these parameters could be used in order to identify patients with intestinal metaplasia, further studies are needed to verify these results.

KEYWORDS : Intestinal metaplasia, helicobacter pylori, fatty liver disease, histopthologic evaluation

INTRODUCTİON:

With large increases in gastric cancer diagnoses in recent decades and advances in novel endoscopic procedures, more subjects are screening for gastric cancer by than ever before. One of the most important gastric precancerous lesion has been reported as gastric intestinal metaplasia (GIM) which is characterised by either enteric or colonic mucosal immigration into the gastric mucosa.

Early diagnosis of atrophic gastritis (AG), GIM, dysplasia leads to improved outcomes but diagnosis is often delayed leading to increased rates of morbidity and mortality. Despite recent progress in endoscopic screening programmes, GIM-related laboratory features poorly understood and recognized (1). Risk factors of GIM has been reported as presence of H. pylori infection, older ages, a smoking history strong spicy food, occupation status and the presence of IL10-592 C/A (2). In this study we explored the possible impact of established GIM on the basic laboratory parameters.

Non alcoholic fatty liver disease (NAFLD) is the condition of increased fat in the liver and can trigger fibrosis and inflammation in the liver, called non-alcoholic steatohepatitis (NASH). Patiens with NASH are at increased risk for cardiovascular events or hepatocellular carcinoma (HCC) (3).

On the other hand, there are a few data regarding gastric effects of NAFLD. So we also aimed to explore the impact of GIM on NAFLD.

MATERİALS AND METHODS:

Between May 2018 and August 2018, we enrolled 85 (40 female; the mean age was 60.8±13.5 years) consecutive patients with GIM. They were assessed for laboratory parameters and underwent hepatobiliary ultrasonography. NAFLD was defined as elevated liver enzymes in the absence of indicators of chronic hepatitis B and C infection and alcohol consumption not exceeding moderate and ultrasonographically detected fatty liver. Serum concentrations of HDL and LDL-cholesterol levels with triglyceride levels which are valid markers of cholesterol syntesis were determined by commercial kits after 12 hours of overnight fasting. Other laboratory parameters were obtained from hospital data. We had previously excluded patients with severe underlying disease, including gastric cancer and gastric resection. Patients who were taking lipid lowering agents, proton pump inhibitors and antidiabetic agents were also excluded from the study. Gastroscopy with biopsy was performed in all patients at enrollment of the study. Control group (123 patients; 60 female; the mean age was 58±14.5 years) was selected from dyspeptic subjects who had no established GIM.

ENDOSCOPY AND HİSTOPATHOLOGİC EVALUATİON

All endoscopic examinations were performed with propophol anestesia with an Fujinon videoscope (Tokyo, Japan) was used. Biopsy samples were reviewed by a pathologist for GIM and H. Pylori status. Macroscopic gastric biopsy specimens has fixed in 10% formalin and had evaluated microscopically with May Grünwald Giemsa, MGG, for H. Pylori and with Haematoxylen and Eosin for intestinal metaplasia. Intestinal metaplasia was classified in two grades (absent or present).

STATİSTİCAL ANALYSİS

All statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.). The demographic clinical and radiologic characteristics of the patients were compared by Student's t-test exact test were used to assess the difference in proportions. All P values are two-sided; significance was indicated by a P value of less than 0.05.

RESULTS

The characteristics of the patients at baseline were well balanced between the study patients and control subjects with respect to age and gender.

Total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglyceride levels were similar in the GIM and control groups. The mean HDL cholesterol level was 47.7±14.1 mg per deciliter in GIM group and was 54.9±58.05 mg per

deciliter in control group (P=0.281). The mean LDL cholesterol level was 120.6±39.7 mg per deciliter in GIM group and was 117.3±37.6 mg per deciliter in control group (P=0.767). GIM group had also similar triglyceride levels compared with control group (153.9±137.2 versus 153.1±85.3, P=0.375).

Whereas the prevalence of NAFLD in patients with GIM was 22±0.4%, the prevalence of NAFLD in control subjects was 25.2±1.1%(P =0.247).

Compared to patients without the GIM, patients with the GIM on admission (N=85;) had lower serum ferritin levels (55±45 versus 112±245 U/L;95% confidence interval 17 to 131, P=0.019).

Most notably, there was a significant differentiation between groups in terms of serum TSH levels (2.07±2.4 versus 4.3±20.4 U/L;95% confidence interval 1.66 to6.29, P=0.042 by Fisher's test).

The difference between GIM group and control subjects with respect to the mean glucose and creatinin levels was also significant (126.5±58.5 versus 108±27.7 milligram per deciliter, P=0.03 and 1.82±8.3 milligram per deciliter versus 0.9±0.8 milligram per deciliter; 95% confidence interval 0.6 to 2.3; P=0.34).

There was a significant difference regarding the ferritin levels between both groups. Whereas ferritin levels in the patients' group with intestinal metaplasia was 55,18 ng/mL ± 45,02, the level in the group without intestinal metaplasia was 112,23 ng/mL ± 245,82; 95% confidence interval 17,27 to 131,38, P=0,019).

There could not testified any difference between the GIM group and the control group regarding HbA1c. The mean HbA1c-value in the GIM group was 6,03±1,53 mmol/mol, respectively 5,81±0,96 in the control group (95 % confidence-interval 0,264 to 0,719; P=0,13).

The other variables were similar across the groups (P=NS).

DİSCUSSİON:

In the current study the rate of H. pylori infection was 56% and did not differ between groups (54% versus 58%). This Turkish single center study exhibits similar results to already published European and Asian studies, and confirms that prevalance of H. Pylori infection is still higher in Middle East as well as in Turkey.

A recent US study involving 4,146 individuals with gastric intestinal metaplasia has showed that the incidence rate of gastric adenocarcinoma was 0.72/1,000 person-years in patients with intestinal metaplasia, with a relative risk of 2.56 compared with the control group (4). Gastric cancer screening with upper gastrointestinal tract endoscopy should be considered in persons who born in high risk areas for gastric cancer (East Asia, Russia, or South America) or who have a family history of gastric cancer. Gastirc screening by endoscopy should be done every 1 to 2 years in patients with findings of atrophic gastritis or intestinal metaplasia on histopathologic examination (5).

Emerging evidence also suggests that preexisting GIM detected by histopathologic examination of the gastric mucosa confers longterm risk of gastric cancer even after the H. pylori infection has been successfully eliminated (6).

In a recent retrospective cohort study involving 923 patients with GIM showed that only family history (hazard ratio, 3.8;95% confidence interval, [1.5–9.7; P (.012)] and extent of GIM (odds ratio, 9.4;95%confidence interval, 1.8–50.4) increased the risk for gastric cancer (7). Due to retrospective nature of the study, we did not obtain that data.

It has been a well known fact that tobacco smoking and many foods including processed, salted or smoked meats are positively associated with noncardia gastric cancer in a dose-dependent manner (8).

Furthermore, multiple risk factors including Helicobacter pylori infection and associated genomics, host genetic factors, environmental milieu, rheumatologic disorders, diet, and intestinal microbiota have a causal relationship for the development of GIM (9). In a case-control, observational study involving 320 patients with functional dyspepsia has revealed that a higher consumption of fruits and vegetables has been a key role to prevent GIM. Furthermore, processed salty foods (e.g., cured meats) have reportedly been related to metaplasia (10). Other hand, an endoscopy-based study suggested that high salt intake could be associated with an increased risk of atrophic gastritis with intestinal metaplasia (11).

Non-Alcoholic Fatty Liver Disease (NAFLD), the accumulation of excess fat within hepatocytes, is increasing in prevalence due to the high-fat western diet. Correlational studies have also implicated vegetable consumption as a preventing factor in NAFLD (12).

NAFLD is a hepatic disease with increased ratio of glucose and triglycerides in the liver, whereas the prevalence of NAFLD positively correlates with obesity. İt is reported that metabolic syndrome and NAFLD are predictors of NASH and hepatocellular carcinoma (13).

The essential treatment consists of weight loss and constant physical effort (14). Besides of weight loss, it is advised that patients should receive a calorie-restricted diet (600 kcal less than a person with the same weight). Further, carbohydrates, saturated fats and soft-drinks should be avoided (15).

There are many studies regarding the increased risk of malignancies related to NAFLD/NASH (16).

Our study is the first hospital-based study of the effect of GIM on NAFLD and we found no link between NAFLD and GIM. Notably, there were no statistically siginificant differences between groups in terms of HDL-C, LDL-C and triglyceride levels. This suggests that there is no effect of GIM on serum lipid profiles as assessed biochemically and ultrasonographically-detected NAFLD and detoriation of lipid profile tests are not potentially useful biomarkers for predicting GIM in Asian subjects.

The pathogenic link between thyroid function and gastric premalign lesions has rarely examined before (17). We showed a clear association between hypothyroidism and GIM. Our data indicate that thyroid metabolism plays a key role in metabolic regulatory axis and is critical in the gastric mucosal damage, endotoxemia, inflammation, and inhibition of gastric mucosal healing, contributing to GIM.

There are only few studies regarding intestinal metaplasia in patients with chronic kidney disease. İn the oldest study of 1989 with 80 patients with chronic renal failure, who were dialysed, were endoscopied and biopsied. 50 Patients (62.5%) had intestinal metaplasia (18).

The risk of dialysis patients to have a bleeding in the upper gastrointestinal tract is higher. This is one of the results of gastrointestinal alterations in patients with chronic renal disease. İn a study of Netto et al. 96 patients with chronic kidney disease were endoscopied as preparation for kidney transplantation. Most frequent found gastric disorder was a pangastritis (57.30%). Erosive Pangastritis was found with 30.2 %. Gastric metaplasia was found in 8.33 %, which is much less than in the study of 1989 (19). Another study with 50 chronic renal failure patients and 50 control patients revealed intestinal metaplasia in 29.4 % of the patients in the renal failure group. As conclusion, a higher urea concentration in the gastric juice and following metabolic disorders were regarded as causative for the higher frequency of gastrointestinal alterations compared with patients with normal renal function (20).

There are only few studies concerning gastric atrophy and diabetes as there is reported that patients with gastric atrophy had a lower risk of diabetes (21), direct studies regarding a possible relationship

between intestinal metaplasia and diabetes mellitus do not exist, but a relation between diabetes mellitus and precancerous lesions seems to play a role. As in literature, the interpretation of the HbA1c-values showed no significant difference between the both groups.

İn a study of Gong et al. analysing 4 case-control studies and 9 cohort studies it was concluded, that patients with type 2 diabetes mellitus had a significantly higher risk of cancer, in this meta-analysis concerning oral cancer (22).

On the other side, Saini et al. could show that a 45 % of 420 patients with type 2 diabetes mellitus had one or more oral lesions, respectively 38,3 % in the group of non-diabetic patients (420 patients). However, these were benign lesions, eg. geographic tongue, denture stomatitis and angular cheilitis Precancerous lesions (lichen planus) was found in two diabetic patients, respectively no patients in the control group, so none association between precancerous lesions and diabetic patients was found (23). In conclusion of the meta analysis, mentioned above, a relationship between patients with type 2 diabetes mellitus and precancerous lesions and perhaps intestinal metaplasia has to be hypothesized. The data above suggest that both hyperglicemia and renal dysfunction alter gastric mucosal tissue with formation of toxic products, which may play a potential pathogenic role in GIM.

İn relation to the significant lower ferritin levels in the group with intestinal metaplasia in contrast to the control group there are not any data in literature. There is only one study in pediatric patients with iron deficiency anemia, where autoimmune gastritis has to be analysed, as hypothesized by the authors (24). İn a study including 456 gastric adenocarcinoma Fonseca-Nunes et al showed that higher serum iron and ferritin stores were not associated with an increased risk of gastric cancer (25). There are several important limitations of the study. First, our study was retrospective and had a small sample size. Second, we did not perform liver biopsy to diagnose for NAFLD. Third, we did not assess thyroid antibodies.

On the other hand, the current study is the first to show the connection between NAFLD and GIM.

Conclusion: Assessing basic laboratory parameters with in this study could serve as simple clinical tool to identify patients at risk for GIM as well as further gastric cancer. Given the previously reported GIM prevalence, full hematologic and biochemical screening may reveal substantial numbers of subjects with previously unknown GIM. To our knowledge this is also the first study to suggest that presence of GIM is not related to NAFLD as well as lipid parameters.

Table 1: Group Statistics İntestinal Metaplasia (0=not Present, 1= Present)

Parameters	İntestinal metaplasia	Number, N	Mean	Standard deviation	Standard mean error
Age (years)	,00	123	54,5447	14,56993	1,31373
	1,00	85	60,8235	13,55779	1,47055
WBC (109/L)	,00	123	7,2485	2,44639	,22058
	1,00	85	7,4640	3,10400	,33668
Neu (109/L)	,00	123	12,1974	19,10736	1,72285
	1,00	85	44,7313	25,78600	2,79688
Hgb (g/dl)	,00	123	13,2130	1,90366	,17165
	1,00	85	12,9518	2,04512	,22182
Hct (%)	,00	123	40,4480	5,05667	,45594
	1,00	85	40,0035	5,87060	,63676
MCV (fL)	,00	123	86,6154	5,98210	,53939
	1,00	85	86,9459	6,83831	,74172
PLT (109/L)	,00	123	252,0894	75,51886	6,80931
	1,00	85	244,2459	75,75930	8,21725
Glucose (mg/dl)	,00	120	108,0083	27,74600	2,53285
	1,00	82	126,5732	58,50969	6,46131
Urea (mg/dl)	,00	118	33,1864	21,28960	1,95987
	1,00	84	36,1905	23,80770	2,59763
Creatinine (mg/dl)	,00	121	,9389	,80066	,07279
	1,00	85	1,8253	8,38333	,90930
AST (U/L)	,00	119	21,8571	9,09114	,83338
	1,00	82	24,2317	32,24455	3,56081
ALT (U/L)	,00	121	20,1736	13,41683	1,21971
	1,00	84	22,6310	27,76484	3,02939
Albumin (g/dl)	,00	84	4,4562	,57878	,06315
	1,00	60	4,5283	,41745	,05389
ALP (U/L)	,00	89	83,2135	37,35714	3,95985
	1,00	57	83,7719	31,02419	4,10925
GGT (U/L)	,00	89	26,0337	22,78429	2,41513
	1,00	56	33,0357	41,04010	5,48421
Triglycerids	,00	103	153,1650	85,38426	8,41316
	1,00	71	153,9014	137,24890	16,28845
HDL (mg/dl)	,00	100	54,9200	58,05252	5,80525
	1,00	69	47,7826	14,12015	1,69987
LDL (mg/dl)	,00	98	117,3673	37,68463	3,80672
	1,00	69	120,6812	39,77602	4,78847
Cholesterol (mg/dl)	,00	102	195,5196	46,30500	4,58488
	1,00	72	197,4861	51,98212	6,12615
Ferritin (ng/ml)	,00	69	112,2357	245,82435	29,59377
	1,00	44	55,1807	45,02341	6,78753
TSH (µlU/ml)	,00	109	2,0713	2,43628	,23335
	1,00	75	4,3889	20,87370	2,41029
HbA1c (%)	,00	57	5,8104	,96586	,12793
	1,00	46	6,0380	1,53358	,22611

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