Gastrointestinal Bleeding Risk Factors in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To investigate the factors leading to the development of gastrointestinal bleeding (GIB) by comparing patients with diabetes mellitus Type 2 (T2DM) with dyspeptic complaints without GIB; and patients with T2DM who had GIB, regardless of the presence of *helicobacter pylori.*

Study Design: Analytical study.

Place and Duration of Study: Department of Endocrinology and Gastroenterology, Faculty of Medicine, Karadeniz Technical University, from January 2018 to June 2019.

Methodology: The patients were divided into GIB and dyspepsia groups. After the identification of patients in both groups, demographic characteristics, drugs, comorbidities, presence of diabetic macro- and micro-vascular complications, and endoscopic findings were examined retrospectively for each patient.

Results: There were 106 patients, with 53 patients in each group. Mean age was significantly higher in the GIB group compared to the dyspepsia group ($p<0.001$). Body mass index (BMI) was significantly lower in the GIB group ($p<0.001$). Frequency of congestive heart failure (CHF), chronic kidney disease (CKD), and cerebrovascular disease (CVD), heart valve disease, and cardiac arrhythmia was significantly higher in GIB group ($p <0.05$ for all). No significant correlation was found between acetylsalicylic acid (ASA) use and GIB ($p=0.103$). The use of nonsteroidal anti-inflammatory drugs (NSAID), novel oral anticoagulants (NOAC), and clopidogrel was significantly higher in the GIB group ($p=0.032$, $p=0.031$, and $p=0.032$, respectively). Proton pump inhibitor (PPI) use was significantly higher in the dyspepsia group ($p=0.002$).

Conclusion: Age, and poly medications were associated with increased frequency of GIB. The use of ASA, when not administered with other agents that may induce GIB, does not increase the risk of developing GIB in obese T2DM patients younger than 65 years of age, who have increased HbA1c levels.

Key Words: *Type 2 diabetes mellitus, Dyspepsia, Gastrointestinal bleeding, Acetylsalicylic acid, Risk factors, Obesity, Medication*.

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INTRODUCTION

Cardiovascular diseases are the most common cause of mortality in patients with diabetes mellitus type 2 (T2DM); and the American Diabetes Association (ADA) guidelines recommend the initiation of low dose acetylsalicylic acid (ASA) in diabetic patients with cardiovascular risk factors after evaluating the benefit-harm ratio in detail.[1]

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In addition, patients with T2DM have an increased risk of gastrointestinal bleeding (GIB) following the use of ASA compared to non-diabetic patients.[2]

Administration of *helicobacter pylori* (Hp) eradication to reduce the risk of GIB in patients scheduled for ASA administration remains controversial.[3] Despite varying among societies, there are numerous limiting factors for Hp eradication, including high rate of positivity, difficult eradication, and the risk of re-infection.[4-6] For this reason, as a more practical solution, proton pump inhibitors (PPI) can be used for GIB prophylaxis in patients scheduled for ASA administration.[7]

In this study, the aim was to investigate the factors leading to the development of GIB by comparing patients with T2DM who had dyspeptic complaints but had no GIB; and patients with T2DM who had GIB, regardless of the presence of Hp.

METHODOLOGY

The study included patients with T2DM who underwent endoscopy at Karadeniz Technical University, Faculty of Medicine, Gastroenterology Unit, between January 2018 and June 2019. Patients with T2DM who were hospitalised due to major GIB (hematemesis or melena), which was confirmed by hospital personnel and caused by a peptic ulcer lesion as determined in an endoscopic procedure, were included in GIB group. Cases with any other cause of bleeding, in-hospital bleeding, and prior Hp eradication were excluded. For dyspepsia group, patients selected among patients who, with T2DM scheduled for ASA administration and had dyspeptic complaints, and who had undergone gastroscopy. Patients with a history of GIB and Hp eradication were excluded. Medicines used within 72 hours before gastroscopy were recorded for each patient. ASA doses below 300 mg were accepted as low dose. The GIB group was formed from the intersection of ICD codes for gastrointestinal hemorrhage (K92) and T2DM (E11).

Data were analysed using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp.). Categorical variables were expressed as frequencies (n) and percentages (%) and continuous variables were expressed as median and minimum-maximum values mean and standard deviation for normally distributed, and median with IQR for non-normally distributed. Categorical variables were compared using Chi-square test and Fisher's Exact test. Independent continuous variables were compared using Student t-test when normal distribution condition was met, and Mann-Whitney U-test when not. Independent continuous variables were compared using Student t-test when they show a normal distribution and Mann-Whitney U-test when they did not show a normal distribution. A p-value of <0.05 was considered significant.

RESULTS

Initially, there were 53 patients; in the T2DM group and 56 patients in the GIB group. The three youngest patients in the dyspepsia group were excluded from the study and the remaining 53 patients who were closest to the GIB group in terms of age, were included in the study.

Table I presents the demographic characteristics and comorbidities of the patients. Mean age was above 60 years in both groups, while it was significantly higher in the GIB group compared to the Dyspepsia group ($p<0.001$). Body mass index (BMI) was significantly lower in the GIB group ($p<0.001$). Frequency of congestive heart failure (CHF), chronic kidney disease (CKD), and cerebrovascular disease (CVD), heart valve disease, and cardiac arrhythmia was significantly higher in GIB group ($p<0.05$ for all).

Table II presents the drugs used by the patients. No significant correlation was found between ASA use and GIB ($p=0.103$). In the GIB group, 11 out of 23 patients using ASA were receiving second agents that could cause a GIB. Isolated use of ASA was noted in 12 (23%) patients in the GIB group and in 14 (26%) patients in the dyspepsia group. In the comparison of patients using ASA only, no significant correlation was found between ASA use and GIB ($p=0.821$). After excluding patients using PPI from patients who used ASA only, there were 9 (17%) patients in the GIB group and 7 (13%) patients in the dyspepsia group. In these patients, no significant correlation was found between ASA and GIB ($p=0.776$). The number of patients using anticoagulants and/or antithrombotics and/or nonsteroidal anti-inflammatory drugs (NSAID) was significantly higher in the GIB group ($p<0.001$). Moreover, the use of NSAID, novel oral anticoagulants (NOAC), and clopidogrel was significantly higher in the GIB group ($p=0.032$, $p=0.031$, and $p=0.032$, respectively). In the GIB group, 4 out of 15 patients using multiple agents that could cause GIB were using PPI; whereas, no patient in the dyspepsia group was using multiple drugs that could cause GIB. No significant relationship was found between metformin and insulin use and GIB ($p=0.181$ and $p=0.231$, respectively). PPI use was significantly higher in the dyspepsia group ($p=0.002$). In the dyspepsia group, 9 (69%) out of 13 patients with CAD were using PPI; while in the GIB group, only 7 (32%) out of 22 patients with CAD were using PPI. In the dyspepsia group, 30 patients were using PPI, while 12 of them were using an agent that could cause GIB. In the GIB group, 13 patients were using PPI and 43 patients were using an agent that could cause GIB.

Table III presents the laboratory parameters of the patients. HbA1c values were similar in both groups ($p=0.073$).

DISCUSSION

The results indicated that the use of low-dose ASA alone does not increase the prevalence of GIB. It was also revealed that age and additional comorbidities are the primary factors causing increased prevalence of GIB.

Fujimoto *et al.* analysed the clinical data of 13 million patients aged 20–74 years and found that upper gastrointestinal system bleeding was most common in males and in individuals aged 60–74 years.[8] Similarly, in this study, advanced age was associated with a significant increase in the development of GIB. Of note, 87% (n=46) of the patients with GIB were aged over 60 years and 70% (n=37) of them were aged over 65 years. Moreover, 58.5% of the patients with GIB were males, which was at the limit of significance when compared to the dyspepsia group ($p=0.052$).

Chi *et al.* evaluated NSAID-related GIB in hospitalised patients aged over 60 years and reported that history of cardiovascular and cerebrovascular disease, DM, antiplatelet drugs, upper abdominal discomfort, anorexia and NSAID used for 0.5 to 3 months were associated with GIB.[9] Similarly, in this study, the prevalence of GIB was significantly higher in patients with lower BMI. Additionally, as seen in Table I, the risk of GIB increased as the prevalence of comorbidities increased, except for chronic obstructive pulmonary disease (COPD) and CAD. Nevertheless, the limited number of patients with COPD in both groups may not provide a clear evaluation regarding this issue. On the other hand, no significant difference was found between the two groups with regard to the number of

patients with CAD, although the number of patients with CAD was higher in the GIB group. This finding could be due to higher rate of PPI use in the dyspepsia group (Table II). The use of both antithrombotics and PPI have increased over recent years.[8] The protective efficacy of PPI against GIB is known;[7,10,11] whereas, many reservations have been noted in the literature regarding their long-term use.[12] In addition, a newly published meta-analysis reported that long-term use of PPI increases the risk of developing gastric cancer.[13]

Table I: Demographic and clinical characteristics.

Variables		Groups		*p*
		GIB (n=53)	Dyspepsia (n=53)	
Age (year)†		70 (24-89)	62 (35-78)	<0.001*
Sex	Male	31 (58.5)	21 (39.6)	0.052**
	Female	22 (41.5)	32 (60.4)	
Weight (kg)†		75 (50-120)	85 (65-117)	0.001*
BMI (kg/m^2)†		27.5 (18.4-42.5)	32.7 (23.0-46.3)	<0.001*
Duration of diabetes (years)†		8 (1-28)	10 (2-34)	0.077*
Smoking‡	Yes	4 (7.5)	3 (5.7)	1.000***
	No	49 (92.5)	50 (94.3)	
Hypertension‡	Yes	38 (71.7)	37 (69.8)	1.000**
	No	15 (28.3)	16 (30.2)	
CAD‡	Yes	22 (41.5)	13 (24.5)	0.098**
	No	31 (58.5)	40 (75.5)	
CHF‡	Yes	13 (24.5)	0 (0.0)	<0.001**
	No	40 (75.5)	53 (100.0)	
CKD‡	Yes	16 (30.2)	6 (11.3)	0.031**
	No	37 (69.8)	47 (88.7)	
CVD‡	Yes	10 (18.9)	2 (3.8)	0.032**
	No	43 (81.1)	51 (96.2)	
COPD‡	Yes	4 (7.5)	3 (5.7)	1.000***
	No	49 (92.5)	50 (94.3)	
Heart valve disease‡	Yes	6 (11.3)	0 (0.0)	0.027***
	No	47 (88.7)	53 (100.0)	
Arrhythmia‡	Yes	11 (20.8)	1 (1.9)	0.006**
	No	42 (79.2)	52 (98.1)	

*‡n (%),†:median [min-max. *: Mann-Whitney U-test. **: Chi-square test. ***: Fisher's Exact test. GIB: Gastrointestinal bleeding, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease.*

Table II: Medicines used by the patients.

Variables		Groups		*p*
		GIB‡ (n=53)	Dyspepsia‡ (n=53)	
Aspirin	Yes	23 (43.4)	14 (26.4)	0.103*
	No	30 (56.6)	39 (73.6)	
Warfarin	Yes	7 (13.2)	1 (1.9)	0.060**
	No	46 (86.8)	52 (98.1)	
LMWH	Yes	1 (1.9)	0 (0.0)	1.000**
	No	52 (98.1)	53 (100.0)	
Clopidogrel	Yes	10 (18.9)	2 (3.8)	0.032*
	No	43 (81.1)	51 (96.2)	
NOAC	Yes	8 (15.1)	1 (1.9)	0.031**
	No	45 (84.9)I	52 (98.1)	
NSAID	Yes	10 (18.9)	2 (3.8)	0.032*
	No	43 (81.1)	51 (96.2)	
Multiple anticoagulant or antithrombotic	Yes	15 (28.3)	0 (0.0)	<0.001*
	No	38 (71.7)	53 (100.0)	
Any anticoagulant or antithrombotic	Yes	43 (81.1)	19 (35.8)	<0.001*
	No	10 (18.9)	34 (64.2)	
Steroids	Yes	0 (0.0)	4 (7.5)	0.118**
	No	53 (100.0)	49 (92.5)	
Steroids + NSAID	Yes	0 (0.0)	6 (11.3)	0.027**
	No	53 (100.0)	47 (88.7)	
Metformin	Yes	36 (67.9)	43 (81.1)	0.181*
	No	17 (32.1)	10 (18.9)	
Insulin	Yes	36 (67.9)	29 (54.7)	0.231*
	No	17 (32.1)	24 (45.3)	
PPI	Yes	13 (24.5)	30 (56.6)	0.002*
	No	40 (75.5)	23 (43.4)	

*‡n (%). *: Chi-square test. **: Fisher's Exact Test. GIB: Gastrointestinal bleeding, LMWH: Low-molecular-weight heparin, NOAC: Novel oral anticoagulants, NSAID: Nonsteroidal anti-inflammatory drugs, PPI: Proton pump inhibitors.*

Table III: Laboratory parameters.

Variable	Groups		*p*
	GIB (n=53)	Dyspepsia (n=53)	
HbA1c (%)[¥]	6.7 (4.8-10.2)	7.0 (5.4-15.4)	0.073[**]
Creatinine[¥]	1.1 (0.6-7.5)	0.8 (0.4-4.0)	<0.001[**]
Albumin[¥]	3.3 (1.9-4.5)	4.1 (1.9-4.8)	<0.001[**]
BUN[¥]	47 (14-173)	16 (9-90)	<0.001[**]
ALT[¥]	14 (3-72)	15 (3-93)	0.229[**]
LDH[¥]	202 (92-900)	186 (125-514)	0.099[**]
WBC[¥]	10430 (1178-58370)	7600 (3720-13800)	<0.001[**]
PNL[¥]	7190 (2140-46570)	4280 (1780-9900)	<0.001[**]
Lymphocyte[¥]	1610 (470-6610)	2280 (590-4140)	0.007[**]
Hgb[†]	9.4±2.8	12.6±1.9	<0.001[*]
PLT[†]	206484.9±79902.1	246792.5±58636.2	0.004[*]
MPV[¥]	10.1 (7.0-13.6)	10.5 (7.9-13.7)	0.013[**]
CRP[¥]	0.7 (0.0-8.6)	0.4 (0.1-7.1)	0.042[**]

*[†]: mean ± standard deviation,[¥]:median [min-max]. *: Independent Samples t-test. **: Mann-Whitney U-test. GIB: Gastrointestinal bleeding, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, WBC: White blood cell count, PNL: Polimorpho nuclear leukocyte, Hgb: Hemoglobin, PLT: Platelet, MPV: Mean platelet volume, CRP: C-Reactive Protein.*

In this study, the analysis of four patients that were using prophylactic PPI while using multiple agents that could cause GIB indicated that PPI treatment did not show adequate efficacy in preventing GIB, while using multiple agents that could cause GIB.

In this study, the rate of ASA use was higher in the GIB group, though no significant difference was established (p=0.103). Moreover, after excluding agents that could cause GIB other than ASA, it was observed that the use of ASA did not lead to a significant increase in the risk of GIB, regardless of the use of PPI. In ASCEND-P, 15480 patients with T2DM without significant cardiovascular disease were randomised to aspirin 100 mg once daily or placebo; and the results indicated that major bleeding occurred in 314 (4.1%) patients using aspirin and in 245 (3.2%) patients using placebo (p=0.003). Additionally, a significant portion (25%) of the major bleedings described in the study occurred in the upper GI tract. In the same study, upper GI endoscopy was performed in 195 (2.5%) patients in the ASA group and in 205 (2.6%) patients in the placebo group due to dyspeptic complaints.[14] The fact that the number of patients who needed upper GI endoscopy was similar, could be considered as an indirect indicator that the use of ASA does not cause an increase in dyspeptic symptoms. Another cohort study evaluated 186,425 individuals and suggested that the use of aspirin was associated with the risk of major bleeding in most of the subgroups studied; and that the use of ASA in individuals with DM did not increase the risk of bleeding.[15] When evaluated in light of the findings, the findings of the authors suggest that the use of ASA increases the risk of GIB. However, this outcome cannot be attributed to the use of ASA alone. Comorbidities and concomitant medications are additional factors leading to the development of GIB. The findings of this study showed that the use of ASA did not cause a serious risk in GIB development, particularly in obese patients, and individuals younger than 65 years of age, and patients with high HbA1c values.

Although T2DM is a prothrombotic condition, there are reports that T2DM is an independent risk factor for GIB.[15,16] In this study, HbA1c values were similar between the two groups, which suggests that GIB is independent of the severity of T2DM. This study was limited due to its retrospective data collection and small patient population.

CONCLUSION

The use of ASA, when not administered with other agents that may induce GIB, does not increase the risk of developing GIB in obese T2DM patients, younger than 65 years of age, who have increased HbA1c levels. Instead of initiating prophylactic ASA in each patient, it would be wiser to initiate ASA after considering individual characteristics and risk factors of the patients.

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ETHICAL APPROVAL:
The study protocol was approved by Karadeniz Technical University, Ethics Committee (24237859-491).

PATIENTS' CONSENT:
Consent forms were taken from the patients before endoscopic procedure.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
SVK: Conception and design of work, analysis and inter-pretation of data, drafting and revision of work.
IH: Conception and drafting of the work.
YEG: Design and revision of the work.
SD: Conception of work, analysis and interpretation of data revision.
SK: Design of work, interpretation of data, and revision of the work.

SF: Conception of work, analysis and interpretation of data and revision of work.
All authors gave final approval of the version to be published, agreed to be accountable for all aspects of the work.

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