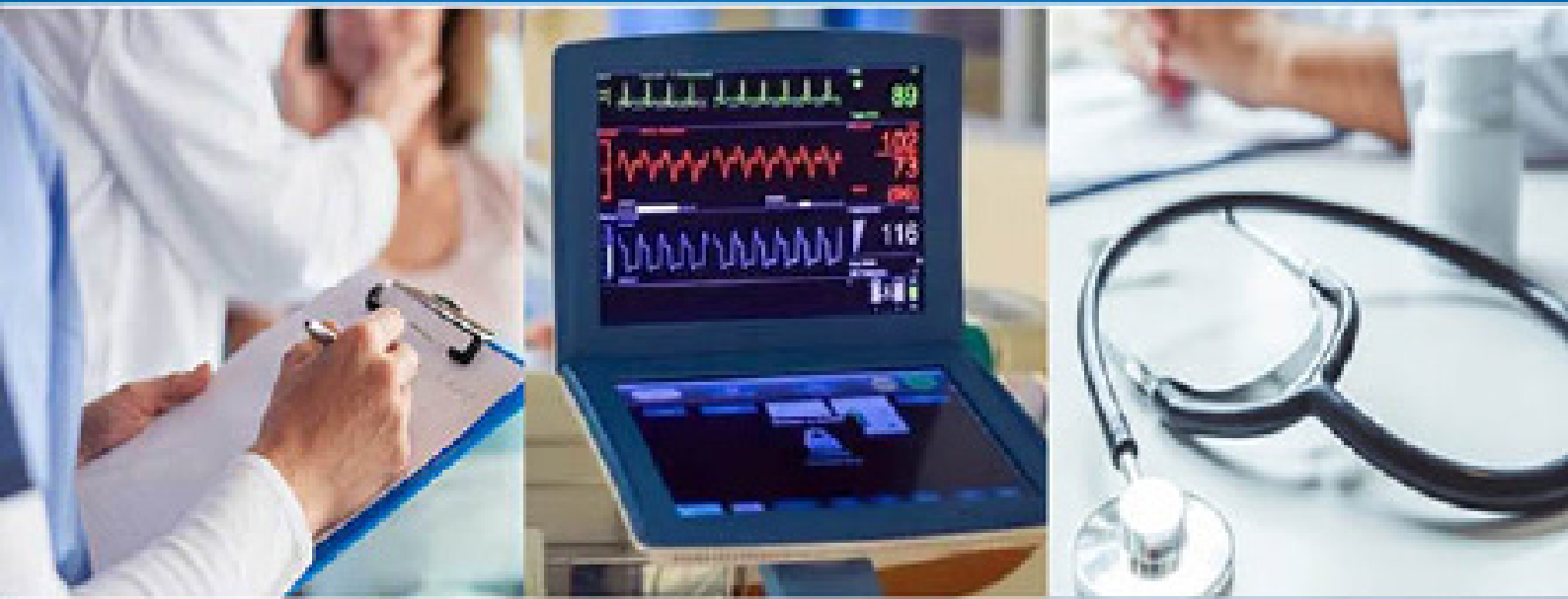


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Volume: 4 Issue: 4 Year: 2026

ORIGINAL ARTICLES

The effect of SGLT2 inhibitors on volume-related laboratory and metabolic parameters in older adults: a 6-month retrospective study..... 76-83
Hacıömeroğlu A, Çifci A, Öztürk ZN, Varlıbaş A, Çirakoğlu Ş.

Knowledge, attitudes, and practices of medical students regarding adult immunization: a cross-sectional study 84-90
Taştan M, Artıran İğde FA.

Clinicopathological characteristics of gastric polyps in a *Helicobacter pylori*-endemic region: a real-world cohort study 91-95
Çakal B, Polat YH.

LETTER TO THE EDITOR

Acute uric acid nephropathy during DA-EPOCH-R therapy in primary mediastinal large B-cell lymphoma..... 96-97
Özyurt MB, Çalış U, Çelik S, Güneş A, Kurt Yüksel M.

Reevaluating long-term proton pump inhibitor safety: potential metabolic drug interactions and personalized prescribing 98-99
Sher SAR.

The effect of SGLT2 inhibitors on volume-related laboratory and metabolic parameters in older adults: a 6-month retrospective study

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ABSTRACT

Aims: This study evaluated the effects of sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy on volume-related laboratory parameters, blood pressure, and pulse rate in geriatric patients with type 2 diabetes (T2D) mellitus without major comorbidities.

Methods: This retrospective study included patients aged ≥ 65 years with isolated T2D who initiated SGLT2 inhibitor therapy for the first time. Patients with hypertension, cardiovascular disease, chronic kidney disease, or diuretic use were excluded. Hematological, renal, biochemical, and electrolyte parameters, together with systolic (SBP) and diastolic blood pressure (DBP) and pulse rate, were assessed before treatment and after 3 and 6 months. Repeated-measures parametric or non-parametric tests were used as appropriate.

Results: Among 206 patients, 190 received dapagliflozin and 16 empagliflozin. Body weight, body-mass index (BMI), waist circumference, and blood pressure decreased significantly ($p < 0.001$). Renal function markers (urea, creatinine, and blood urea nitrogen [BUN]/creatinine ratio) increased, whereas estimated glomerular filtration rate (eGFR) decreased. Sodium and albumin levels increased, while uric acid levels decreased (all $p < 0.001$). Significant reductions were observed in glucose and HbA1c levels. Triglycerides (TG) decreased, whereas total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol increased. Hemoglobin, hematocrit, red blood cell (RBC), and platelet counts increased significantly ($p < 0.001$). Most changes were more pronounced during the first 3 months and then approached a plateau.

Conclusion: SGLT2 inhibitors improved anthropometric measures, blood pressure, hematological indices, and glycemic control in geriatric patients without comorbidities. Early changes in volume-related parameters highlight the importance of close monitoring during treatment initiation while supporting the safe and effective use of SGLT2 inhibitors in this population.

Keywords: Aged, diabetes mellitus; type 2, sodium-glucose transporter 2 inhibitors, water-electrolyte balance, uric acid

INTRODUCTION

Type 2 diabetes (T2D) mellitus is a chronic condition whose prevalence is steadily increasing in the elderly population and which is closely associated with morbidity. Age-related physiological changes, reduced renal reserve, and fragility in fluid-electrolyte balance in geriatric patients necessitate particular attention when selecting antidiabetic treatment. In this patient group, ensuring glycemic control is as clinically important as the close monitoring of potential treatment-related side effects and hemodynamic changes.^{1,2}

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are antidiabetic agents that improve glycemic control by reducing the reabsorption of glucose and sodium in the proximal renal tubule; their clinical use has been increasing in recent years. These agents may cause a reduction in intravascular volume via osmotic diuresis and natriuresis; consequently, a decrease in blood pressure, an increase in hematocrit levels,

and changes in certain volume-related laboratory parameters may be observed.^{3,4}

The volume-reducing effects of SGLT2 inhibitors may give rise to concerns regarding hypotension, dehydration, and changes in renal function, particularly in elderly patients. The vast majority of studies in the current literature evaluating the efficacy and safety of these agents have included patient groups with additional comorbidities such as hypertension, heart failure, or chronic kidney disease. This situation results in limited data on the volume-related effects of SGLT2 inhibitors in geriatric individuals with a diagnosis of diabetes alone and no additional systemic disease.^{5,6}

The aim of this study is to retrospectively evaluate the effects of SGLT2 inhibitor therapy on volume-related laboratory parameters and vital signs, such as blood pressure and heart rate, in geriatric patients with T2D without comorbidities

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at baseline, 3 months, and 6 months. The aim is to provide a clearer understanding of the effects of SGLT2 inhibitors on volume status in an elderly and selected patient group.

METHODS

Ethics

This study was approved by the Non-interventional Researches Ethics Committee of Kırıkkale University (Date: 27.11.2024, Decision No: 2024.11.20). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection and Inclusion/Exclusion Criteria

This study was designed as a single-center, retrospective, observational study. The study was conducted by reviewing the electronic medical records of patients followed at the Department of Internal Medicine, Kırıkkale University Faculty of Medicine Hospital, between 2023 and 2024.

Inclusion criteria: Patients aged ≥ 65 years who were initiated on SGLT2 inhibitor therapy for the first time due to T2D were included in the study. Complete follow-up data from the pre-treatment period and through at least the sixth month of SGLT2 inhibitor therapy were required for study inclusion.

Exclusion criteria: Patients with chronic conditions, including hypertension, coronary artery disease, heart failure, atrial fibrillation, or chronic kidney disease (estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²), those receiving any long-term medication other than oral antidiabetic agents, those treated with insulin, those with an active infection, a history of hospitalization within the preceding 3 months, or a history of acute kidney injury or dehydration requiring hospitalization within the preceding 6 months were excluded. Current smokers, alcohol users, and patients receiving diuretic therapy were also excluded. Furthermore, patients who were diagnosed with any new chronic disease, initiated on any medication other than oral antidiabetic agents, or experienced an acute infection during the 6-month follow-up period were excluded from the final analysis.

A total of 206 patients meeting these criteria were included in the study. Of these, 190 were receiving dapagliflozin, and 16 were receiving empagliflozin.

Study Design

Demographic data for patients, as well as laboratory and vital signs data prior to SGLT2 inhibitor treatment and at 3 and 6 months into treatment, were obtained from electronic patient records. The laboratory parameters examined were as follows: hemoglobin, hematocrit, blood urea nitrogen (BUN), creatinine, BUN/creatinine ratio, sodium, potassium, and uric acid levels. Vital signs assessed included systolic (SBP) and diastolic blood pressure (DBP) and pulse rate. The vast majority of SGLT2 inhibitors used were dapagliflozin.

Venous blood samples were collected from the participants at the time of admission and after an 8-hour fast. Blood samples collected for serum-based tests were placed in serum separation tubes, allowed to clot at room temperature for 1 hour, and then centrifuged at 1000×g for 20 minutes. Following serum separation, biochemical and hormonal parameters were analyzed immediately using an automated analyzer.

Samples for complete blood count (CBC) analyses were collected in EDTA tubes. All blood samples were analyzed at the Biochemistry Laboratory of Kırıkkale University.

In our study, serum levels of 25-hydroxy vitamin D, ferritin, thyroid-stimulating hormone (TSH), and free thyroxine (free T4) were measured using the electrochemiluminescence immunoassay (ECLIA) method on the Cobas 8000 e801 analyzer (Roche Diagnostics, Japan, 2019). C-reactive protein (CRP), fasting plasma glucose (FPG), BUN, creatinine, sodium, potassium, calcium, phosphorus, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides (TG), total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were measured photometrically using the Cobas 8000 c702 analyzer (Roche Diagnostics, Japan, 2018). The CBC was performed using the BC-6800 Auto Hematology Analyzer (Mindray, Hong Kong, 2018) based on the SF Cube method for white blood cells and subtypes, DC impedance for platelet count, and colorimetric method for hemoglobin. HbA1c was measured using the high-performance liquid chromatography (HPLC) method on the Premier Hb9210 device (Trinity Biotech, USA, 2020).

In the study, the patients' age (years), height (cm), and body weight (kg) were measured. Based on these data, the body-mass index (BMI) (kg/m²) was calculated. BMI was calculated by dividing the participants' body weight in kilograms by the square of their height in meters. Additionally, the participants' waist circumference (cm) was recorded. Waist circumference measurement was taken while standing upright on a flat surface, by measuring the circumference at the level of the midline, just above both anterior superior iliac spines and aligned with the umbilicus. SBP and DBP measurements, along with pulse rate, were obtained in the seated position using a validated automatic device; pulse was recorded as beats per minute. The data were recorded on patient forms.

Statistical Analysis

All data were analyzed using SPSS version 27.0. The mean and standard deviation were calculated for numerical variables. The Shapiro–Wilk test was used to assess whether the data were normally distributed, and the appropriate statistical method was determined. For parameters showing changes over time, repeated measures ANOVA was applied to parametric data, and the Friedman test was applied to non-parametric data. When ANOVA or the Friedman test yielded significant results, Bonferroni-corrected post-hoc tests or Wilcoxon signed-rank tests were used for pairwise comparisons. A p-value of < 0.05 was accepted as the level of statistical significance in all tests.

RESULTS

A total of 206 patients meeting the inclusion criteria and without any exclusion criteria were included in the analysis. All patients were aged ≥ 65 years, had T2D mellitus, and were initiated on SGLT2 inhibitor therapy for the first time. Only patients with complete follow-up data for at least 6 months were analyzed.

Before analyzing follow-up outcomes, baseline characteristics were compared to confirm that male and female patients were similar at study entry (Table 1). There were no significant differences between the groups. Although male patients

Table 1. Baseline characteristics of the study population according to gender

Parameter	Total (n=206)	Male (n=62)	Female (n=144)	p value	Cohen's d
Age (years)	71.7±3.4	71.5±3.7	71.7±3.3	0.759	-0.05
Height (cm)	167.1±7.1	168.4±7.3	166.6±6.9	0.094	0.26
DM duration (years)	10.2±3.9	9.9±3.9	10.3±3.8	0.549	-0.09

Data are presented as mean±standard deviation. Comparisons were performed using the independent samples t-test. Effect sizes were calculated using Cohen's d. DM: Diabetes mellitus

tended to be slightly taller, this difference did not reach statistical significance and was associated with a small effect size.

After establishing the comparability of baseline characteristics, changes in body weight, BMI, waist circumference, blood pressure, and pulse were assessed at baseline, 3 months, and 6 months (**Table 2**).

Table 2. Changes in body weight, BMI, waist circumference, blood pressure, and pulse over 6 months of SGLT2 inhibitor therapy

Parameter	Baseline (0 mo)	3 mo	6 mo	p value
Body weight (kg)	76.61±9.55	76.07±9.49	75.68±9.55	<0.001
BMI (kg/m ²)	27.50±3.19	27.28±3.16	27.17±3.20	<0.001
Waist circumference (cm)	69.06±2.07	67.98±2.07	67.60±2.07	<0.001
Systolic BP (mmHg)	108.27±9.38	106.13±9.38	105.53±9.42	<0.001
Diastolic BP (mmHg)	70.28±8.53	68.78±8.63	68.44±8.32	<0.001
Pulse (bpm)	71.02±4.02	71.08±4.19	70.98±4.23	0.110

BMI: Body-mass index, SGLT2: Sodium-glucose cotransporter-2, BP: Blood pressure, bpm: Beats per minute, mo: Month

Body weight, body-mass index (BMI), and waist circumference changed significantly over time. Repeated measures ANOVA demonstrated a significant time effect for body weight ($F(2, 410)=411.30$, $p<0.001$, partial $\eta^2=0.667$), BMI ($F(2, 410)=461.68$, $p<0.001$, partial $\eta^2=0.693$), and waist circumference ($F(2, 410)=44,315.03$, $p<0.001$, partial $\eta^2=0.995$).

SBP decreased significantly over time (Repeated Measures ANOVA: $F(2, 410)=4157.24$, $p<0.001$, $\eta^2=0.953$). Pairwise comparisons revealed significant differences between the 0th and 3rd months, the 3rd and 6th months, and the 0th and 6th months. These results demonstrate that SBP showed a continuous and statistically significant decline over the follow-up period.

Similarly, DBP also decreased significantly over time. A repeated measures ANOVA showed a statistically significant difference between the three time points ($F(2, 410)=1664.25$, $p<0.001$, $\eta^2=0.890$). Pairwise comparisons revealed that all pairwise comparisons (0 vs 3 months, 3 vs 6 months, and 0 vs 6 months) were statistically significant.

Pairwise comparisons of baseline, 3-month, and 6-month measurements were performed using Bonferroni correction and are detailed in **Table 3**.

Groups were compared in terms of hematological parameters (white blood cell count, red blood cell (RBC) count, hematocrit, hemoglobin, platelet count, and neutrophil count), biochemical parameters (urea, creatinine, eGFR,

sodium, potassium, calcium, phosphorus, albumin, and uric acid), glycemic parameters (FPG and hemoglobin A1c), liver enzymes (ALT and AST), and lipid profiles (total cholesterol, LDL, HDL and TGs). Statistically significant differences between the time points were observed in urea, creatinine, BUN/creatinine ratio, eGFR, sodium, albumin, uric acid, FPG, hemoglobin A1c, TGs, HDL, total cholesterol, LDL, platelet count, hemoglobin, RBC, and hematocrit ($p<0.05$ for all). These results are summarized in **Table 4**.

Urea, serum creatinine, BUN/creatinine ratio, and sodium levels showed significant changes over time. Whilst urea levels increased significantly, repeated measures ANOVA revealed a significant time effect for urea ($F(2, 410)=421.70$, $p<0.001$, partial $\eta^2=0.673$). Serum creatinine levels also increased significantly over time, and ANOVA revealed a significant time effect for creatinine ($F(2, 410)=8,371.54$, $p<0.001$, partial $\eta^2=0.976$). Analyses of the BUN/creatinine ratio also revealed a significant time effect using repeated measures ANOVA, with increases observed in all pairwise comparisons ($F(2, 410)=156.94$, $p<0.001$, partial $\eta^2=0.434$). eGFR values, however, decreased significantly over time, with ANOVA results revealing a pronounced time effect for eGFR ($F(2, 410)=5849.826$, $p<0.001$, partial $\eta^2=0.966$). It was observed that the most pronounced decline in eGFR levels occurred during the first 3 months, the rate of decline slowed significantly between the 3rd and 6th months, and this suggested that the treatment effect had reached a plateau during this period. Regarding sodium levels, the Friedman test revealed significant changes ($\chi^2(2)=111.614$, $p<0.001$), and post-hoc Wilcoxon signed-rank tests showed significant increases in all comparisons: 0–3 months, 3–6 months, and 0–6 months.

Serum albumin and uric acid levels showed significant changes over time. Albumin levels showed a statistically significant increase; the Friedman test revealed a significant time effect on albumin ($\chi^2(2)=390.965$, $p<0.001$), and post-hoc analyses demonstrated significant increases in all comparisons: 0–3 months, 3–6 months, and 0–6 months. Uric acid levels, however, decreased significantly over time; the Friedman test revealed a significant time effect on uric acid ($\chi^2(2)=383.665$, $p<0.001$), and post-hoc analyses detected significant decreases in all comparisons: 0–3 months, 3–6 months, and 0–6 months.

Glucose and HbA1c levels decreased significantly over time. The non-parametric Friedman test detected a significant time effect for glucose ($\chi^2(2)=298.670$, $p<0.001$), and post-hoc Wilcoxon tests showed significant decreases in all comparisons: 0–3 months, 3–6 months, and 0–6 months. A significant time effect was also found for HbA1c using the Friedman test ($\chi^2(2)=412.000$, $p<0.001$), and post-hoc analyses revealed significant reductions in all pairwise comparisons. It was observed that the most pronounced decrease in HbA1c and fasting glucose levels occurred in the first 3 months, the rate of decrease slowed significantly between the 3rd and 6th months, and the data suggested that the treatment effect had reached a plateau during this period.

TG, HDL, total cholesterol, and LDL levels showed significant changes over time. TG levels showed a significant time effect in repeated-measures ANOVA ($F(2, 410)=2471.298$, $p<0.001$, partial $\eta^2=0.960$), and post-hoc tests revealed significant decreases in all comparisons between 0–3 months, 3–6 months,

Table 3. Differences in clinical and laboratory parameters showing significant changes over time (0–3 months, 3–6 months, and 0–6 months)

Parameter	0 vs 3 mo			3 vs 6 mo			0 vs 6 mo		
	Mean Diff	95% CI	p-value	Mean Diff	95% CI	p-value	Mean Diff	95% CI	p-value
Body weight (kg)	-0.544	-0.628--0.460	<0.001	-0.383	-0.465--0.302	<0.001	-0.927	-0.996--0.859	<0.001
BMI (kg/m ²)	-0.219	-0.248--0.190	<0.001	-0.118	-0.145--0.091	<0.001	-0.337	-0.362--0.311	<0.001
Waist circumference (cm)	-1.074	-1.088--1.060	<0.001	-0.380	-0.387--0.373	<0.001	-1.454	-1.469--1.440	<0.001
Systolic BP (mmHg)	-2.141	-2.199--2.082	<0.001	-0.597	-0.680--0.514	<0.001	-2.738	-2.822--2.653	<0.001
Diastolic BP (mmHg)	-1.505	-1.589--1.421	<0.001	-0.340	-0.420--0.260	<0.001	-1.845	-1.927--1.762	<0.001
Urea (mg/dl)	3.971	3.447--4.494	<0.001	1.150	1.039--1.262	<0.001	5.121	4.563--5.680	<0.001
Serum creatinine (mg/dl)	0.039	0.038--0.039	<0.001	0.018	0.017--0.019	<0.001	0.057	0.056--0.058	<0.001
BUN/creatinine ratio	1.722	1.371--2.073	<0.001	0.275	0.207--0.342	<0.001	1.997	1.632--2.361	<0.001
eGFR	-2.636	-2.717--2.555	<0.001	-0.733	-0.808--0.658	<0.001	-3.369	-3.450--3.288	<0.001
Sodium (mEq/L)*	0.505	–	<0.001	0.393	–	<0.001	0.898	–	<0.001
Albumin (g/dl)*	0.100	–	<0.001	0.100	–	<0.001	0.200	–	<0.001
Uric acid (mg/dl)*	-0.500	–	<0.001	-0.100	–	<0.001	-0.600	–	<0.001
Fasting plasma glucose (mg/dl)*	-20.130	–	<0.001	-2.610	–	<0.001	-22.830	–	<0.001
Hemoglobin A1c (%)*	-0.600	–	<0.001	-0.200	–	<0.001	-0.800	–	<0.001
Triglycerides (mg/dl)	-2.796	-2.897--2.695	<0.001	-1.340	-1.491--1.188	<0.001	-4.136	-4.361--3.911	<0.001
HDL (mg/dl)	1.155	1.062--1.249	<0.001	0.670	0.591--0.749	<0.001	1.825	1.724--1.926	<0.001
Total cholesterol (mg/dl)*	2.000	–	<0.001	1.000	–	<0.001	3.000	–	<0.001
LDL (mg/dl)*	0.600	–	<0.001	0.800	–	<0.001	1.400	–	<0.001
Platelet (10 ³ /μL)*	20.750	–	<0.001	7.250	–	<0.001	28.000	–	<0.001
Hemoglobin (g/dl)	0.753	0.722--0.784	<0.001	0.180	0.147--0.212	<0.001	0.933	0.889--0.976	<0.001
RBC (10 ⁶ /μL)*	0.077	–	<0.001	0.025	–	<0.001	0.102	–	<0.001
Hematocrit (%)	2.182	2.091--2.273	<0.001	0.526	0.428--0.624	<0.001	2.708	2.577--2.840	<0.001

*Diff=median difference. The non-parametric Wilcoxon signed-rank test was applied for these variables. Confidence intervals (CIs) were not reported for the median differences because the standard Wilcoxon signed-rank test procedure used in SPSS does not directly provide 95% CIs for median differences. CI: Confidence interval, p-value: Probability value, BMI: Body-mass index, BP: Blood pressure, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, RBC: Red blood cells, mo: Month

and 0–6 months, with the decline being more pronounced in the 0–3 month period and slower in the 3–6 month period, suggesting a partial plateau trend in TG levels. HDL levels showed a significant time effect in repeated measures ANOVA ($F(2, 410)=950.126$, $p<0.001$, partial $\eta^2=0.903$), and post-hoc tests revealed significant increases in all comparisons; it was observed that the increase was more pronounced during the 0–3 month period and slower during the 3–6 month period and that a partial plateau trend had formed in HDL levels. Total cholesterol and LDL levels showed a significant time effect according to the Friedman test (total cholesterol: $\chi^2(2)=401.080$, $p<0.001$; LDL: $\chi^2(2)=369.592$, $p<0.001$), and post-hoc Wilcoxon tests revealed significant increases in all comparisons; the increases were more pronounced during the 0–3-month period and progressed more slowly in subsequent periods, and a partial plateau trend was observed in both total cholesterol and LDL levels.

Platelet counts, hemoglobin, RBC and hematocrit levels showed a significant increase over time. A significant time effect was detected in platelet and RBC levels using the Friedman test (platelets: $\chi^2(2)=412.000$, $p<0.001$; RBC: $\chi^2(2)=405.813$, $p<0.001$), and post-hoc Wilcoxon tests revealed significant increases in all comparisons between 0–3 months, 3–6 months and 0–6 months. Hemoglobin and hematocrit levels, however, showed a significant time effect when analyzed using repeated measures ANOVA (hemoglobin: $F(2, 410)=2199.486$, $p<0.001$, partial $\eta^2\approx 0.916$; hematocrit: $F(2, 410)=2052.185$, $p<0.001$, partial $\eta^2\approx 0.914$), and post-hoc tests revealed significant increases in all comparisons. No clear

plateau trend was observed in the hemogram parameters. All these findings are summarized in [Table 3](#) and [Table 4](#)

Values showing significant changes over time were identified among the laboratory and clinical parameters monitored. These findings demonstrate the effects of SGLT2 inhibitor use in the study on biochemical and hematological parameters and will be evaluated in the subsequent discussion section in the light of the literature.

DISCUSSION

In the present study, SGLT2 inhibitor therapy in geriatric patients was associated with significant reductions in body weight, BMI, and waist circumference (all $p<0.001$). These changes were most pronounced during the first 3 months of treatment and tended to plateau by the sixth month. Similarly, both SBP and DBP decreased significantly (both $p<0.001$), whereas no significant change was observed in heart rate ($p=0.110$). Consistent with our findings, Lee et al.⁷ reported that SGLT2 inhibitors produced modest but clinically meaningful reductions in body weight, BMI, and blood pressure in geriatric individuals, with effects comparable to those observed in younger adult populations. Likewise, Kanbay et al.⁸ demonstrated clinically significant improvements in these parameters among older adults receiving SGLT2 inhibitor therapy. Thiele et al.⁹ also reported similar findings and suggested that the observed reductions in body weight and BMI were primarily attributable to volume depletion and the mild diuretic effect of SGLT2 inhibitors. In agreement

Table 4. Distribution of groups in terms of hemogram and biochemical parameters

Parameter	Baseline (0 mo)	3 mo	6 mo	p value
Urea (mg/dl)	24.30±6.07	28.27±6.76	29.42±6.83	<0.001
Serum creatinine (mg/dl)	0.67±0.09	0.71±0.10	0.73±0.10	<0.001
BUN/creatinine ratio	17.00±4.14	18.72±4.50	19.00±4.45	<0.001
eGFR	78.05±5.13	75.41±5.20	74.68±5.18	<0.001
Sodium (mEq/L)*	141 (139–142)	141 (140–142)	142 (140–143)	<0.001
Potassium (mEq/L)	4.63±0.40	4.63±0.40	4.63±0.41	0.958
Calcium (mg/dl)*	9.60 (9.35–9.85)	9.60 (9.25–9.95)	9.50 (8.90–10.20)	0.646
Phosphorus (mg/dl)*	3.70 (0.63)	3.70 (0.60)	3.70 (0.60)	0.083
Albumin (g/dl)*	4.60 (0.50)	4.70 (0.40)	4.80 (0.40)	<0.001
Uric acid (mg/dl)*	5.60 (1.40)	5.10 (1.30)	5.00 (1.32)	<0.001
Fasting plasma glucose (mg/dl)*	147.55 (14.35)	127.33 (11.79)	124.72 (14.48)	<0.001
Hemoglobin A1c (%)*	7.50 (0.50)	6.90 (0.50)	6.70 (0.50)	<0.001
CRP (mg/dl)*	1.30 (0.60)	1.30 (0.60)	1.30 (0.73)	0.989
ALT (U/L)*	21.00 (14.00)	21.00 (14.00)	21.00 (14.00)	0.461
AST (U/L)*	17.00 (8.00)	17.00 (8.00)	17.00 (8.00)	0.702
Total cholesterol (mg/dl)*	194 (27)	196 (29)	197 (28)	<0.001
LDL (mg/dl)*	134 (32.95)	134.6 (33.65)	135.4 (33.20)	<0.001
HDL (mg/dl)	44.99±8.07	46.14±8.27	46.81±8.31	<0.001
Triglycerides (mg/dl)	85.79±6.97	82.99±6.82	81.66±6.45	<0.001
White blood cells (x10 ³ /μL)	7.27±1.09	7.27±1.10	7.27±1.11	0.856
RBC (10 ⁶ /μL)*	4.48 (0.39)	4.54 (0.36)	4.56 (0.35)	<0.001
Hematocrit (%)	38.76±2.37	40.94±2.41	41.46±2.59	<0.001
Hemoglobin (g/dl)	13.38±0.76	14.14±0.76	14.32±0.78	<0.001
Platelet (10 ³ /μL)*	223.50 (44.75)	244.25 (43.88)	251.50 (44.50)	<0.001
Neutrophil (10 ³ /μL)*	4.12 (1.95)	4.15 (2.07)	4.13 (2.02)	0.102

* Non-normally distributed variable, values expressed as median (IQR). Analyzed using Friedman test with post-hoc Wilcoxon signed-rank test. All other variables: mean±SD, analyzed using repeated measures ANOVA. mo: month/months, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, RBC: Red blood cells, IQR: Interquartile range, SD: Standard deviation

with the existing literature, our findings indicate that SGLT2 inhibitors induce early and significant improvements in both metabolic and hemodynamic parameters in the geriatric population. When interpreted together with the changes observed in other study parameters, these effects appear to be largely related to volume contraction. Collectively, these findings suggest that the benefits of SGLT2 inhibitors in older adults extend beyond glycemic control and include favorable metabolic and hemodynamic effects. Therefore, careful monitoring of volume status and cardiovascular parameters is warranted during the initiation of SGLT2 inhibitor therapy in geriatric patients.

In the present study, serum urea and creatinine levels increased significantly, whereas eGFR decreased significantly following the initiation of SGLT2 inhibitor therapy (all $p < 0.001$). An et al.¹⁰ reported that the effect of SGLT2 inhibitors on eGFR may vary among individuals; however, the initial decline observed within the first few weeks was followed by stabilization of eGFR over the subsequent months. Similarly, Bay et al.¹¹ demonstrated an early increase in serum urea and creatinine levels accompanied by a decline in eGFR, with these changes stabilizing during follow-up. Groothof et al.¹² likewise reported comparable findings, showing that renal function stabilized over the following months, after which the renoprotective effects of SGLT2 inhibitors became more evident. Furthermore, a meta-analysis by Liu et al.¹³ emphasized that initiation of SGLT2 inhibitor therapy in

geriatric patients may be associated with a rapid decline in eGFR during the first few months of treatment. Consistent with the existing literature, our findings demonstrated that the early increases in serum urea and creatinine levels and the decline in eGFR gradually plateaued by the sixth month of therapy. These observations are likely attributable to the effects of SGLT2 inhibitors on renal hemodynamics and, consequently, intravascular volume status. This finding highlights the importance of close monitoring for potential renal and hemodynamic complications following the initiation of SGLT2 inhibitor therapy, particularly in geriatric patients with reduced renal reserve.

In the present study, FPG and glycated hemoglobin (HbA1c) levels decreased significantly at all follow-up time points, with the most pronounced reductions occurring during the first 3 months of treatment (both $p < 0.001$). Lee et al.⁷ similarly demonstrated that geriatric patients initiated on SGLT2 inhibitor therapy experienced marked early reductions in HbA1c and FPG, with these effects stabilizing during subsequent follow-up. Consistent with these findings, Armentaro et al.¹⁴ reported that both glycemic parameters reached a plateau at approximately 6 months after treatment initiation. Fukuda et al.¹⁵ investigated age-related changes in insulin secretory capacity and the renal glucose threshold in older adults and suggested that SGLT2 inhibitor therapy may be associated with more pronounced, and occasionally variable, glycemic responses during the early phase of treatment in

geriatric patients. In agreement with the existing literature, our study demonstrated a rapid early decline in both FPG and HbA1c levels, followed by a plateau during subsequent follow-up. This pattern is likely attributable to the rapid glucose-lowering effect of SGLT2 inhibitors through enhanced urinary glucose excretion, whereas the subsequent plateau may reflect the establishment of a new steady state resulting from their sustained metabolic and renal hemodynamic effects.

In the present study, serum TG levels decreased significantly, whereas HDL, LDL, and total cholesterol levels increased significantly following SGLT2 inhibitor therapy (all $p < 0.001$). The changes in TG and HDL levels were most pronounced during the first 3 months of treatment, followed by a slower rate of change and a partial plateau between months 3 and 6. In a large meta-analysis, Bechmann et al.¹⁶ reported that the effects of SGLT2 inhibitors on lipid profiles were largely independent of age and were characterized by increases in total cholesterol, LDL cholesterol, and HDL cholesterol, accompanied by a reduction in TG levels. In contrast, Kusunoki et al.,¹⁷ who specifically evaluated geriatric patients receiving SGLT2 inhibitors, observed a significant increase only in HDL cholesterol, whereas no significant changes were detected in the other lipid parameters. Conversely, Şahiner et al.¹⁸ reported significant reductions across all lipid parameters in a cohort of older adults treated with SGLT2 inhibitors. The inconsistent findings reported in the literature may be explained by differences in study design, including sample size, age distribution of the study population, treatment duration, the specific SGLT2 inhibitor used, and variations in concomitant antidiabetic and lipid-lowering therapies. Our findings further suggest that the effects of SGLT2 inhibitors on lipid metabolism in geriatric patients are dynamic and may exhibit substantial interindividual variability. These observations underscore the importance of considering geriatric patient characteristics, treatment duration, and methodological standardization when evaluating the lipid-modifying effects of SGLT2 inhibitors in older adults.

In the present study, serum albumin levels increased significantly following SGLT2 inhibitor therapy ($p < 0.001$). Edwards et al.⁶ similarly reported a significant increase in serum albumin levels among geriatric patients receiving SGLT2 inhibitors. Likewise, Scheen et al.¹⁹ observed increased serum albumin concentrations in a study evaluating older adults treated with SGLT2 inhibitors. In a meta-analysis, Sridharan et al.²⁰ demonstrated that SGLT2 inhibitor therapy was associated with a reduction in albuminuria and suggested that the concomitant increase in serum albumin levels was attributable to both reduced urinary albumin loss and hemoconcentration resulting from plasma volume contraction. Consistent with the existing literature, the increase in serum albumin observed in our study is likely attributable to the plasma volume-reducing effects of SGLT2 inhibitors. This effect may be particularly pronounced in geriatric patients with limited fluid reserves, highlighting the need for careful assessment of volume status during treatment in this vulnerable population.

In the present study, serum uric acid levels decreased significantly following SGLT2 inhibitor therapy ($p < 0.001$). In a cohort study, Habeeb et al.²¹ reported a significant reduction in serum uric acid levels among patients treated with SGLT2 inhibitors. Similarly, Kochanowska et al.²² demonstrated a

significant decline in serum uric acid concentrations in patients receiving SGLT2 inhibitors and suggested that the underlying mechanism was an increase in the tubular secretion of uric acid. Furthermore, a meta-analysis by Yang et al.,²³ which included more than 50 clinical studies, confirmed that SGLT2 inhibitor therapy is consistently associated with reduced serum uric acid levels. Our findings are consistent with the existing literature, demonstrating a significant reduction in serum uric acid levels following SGLT2 inhibitor treatment. Previous studies have further suggested that lower serum uric acid concentrations may be associated with a reduced risk of hypertension and cardiovascular disease, emphasizing the potential clinical relevance of this effect in the geriatric population.^{22,23}

In the present study, serum sodium levels increased significantly following SGLT2 inhibitor therapy ($p < 0.001$). Tang et al.²⁴ similarly reported an increase in serum sodium concentrations associated with SGLT2 inhibitor use. In contrast, Amani-Beni et al.²⁵ observed an increase in serum sodium levels among patients receiving SGLT2 inhibitors; however, the magnitude of this change did not reach statistical significance. Likewise, Cheng et al.²⁶ found no significant changes in serum sodium levels following SGLT2 inhibitor therapy, although they emphasized that sodium homeostasis may be more variable in geriatric patients. Although serum sodium levels increased significantly in our cohort, all values remained within the normal physiological range. The discrepancy between our findings and those reported in previous studies may be attributable to differences in patient characteristics, particularly the inclusion of a very elderly population in our study, who may be more susceptible to volume imbalance and the hemodynamic effects of SGLT2 inhibitor therapy.

In the present study, significant increases in hemoglobin, RBC count, hematocrit, and platelet levels were observed over time (all $p < 0.001$). In the literature, a large-scale meta-analysis by Kanbay et al.,⁸ including patients regardless of age, demonstrated that SGLT2 inhibitor therapy was associated with significant increases in hemoglobin and hematocrit levels. Similarly, Thiele et al.⁹ reported significant elevations in hemoglobin and hematocrit concentrations among patients receiving SGLT2 inhibitors. A meta-analysis conducted by Tian et al.²⁷ also confirmed significant increases in hemoglobin and hematocrit levels in patients treated with SGLT2 inhibitors. Furthermore, a study by Kambara et al.²⁸ focusing specifically on geriatric patients demonstrated a significant association between SGLT2 inhibitor use and increased hemoglobin and hematocrit levels. Consistent with previous studies, our findings suggest that the hematological effects of SGLT2 inhibitors may not be explained solely by diuretic-induced volume contraction and hemoconcentration. In addition to these mechanisms, direct stimulation of erythropoiesis may also contribute to the observed increases in hemoglobin, RBC count, and hematocrit levels.

In this study, SGLT2 inhibitor therapy was associated with significant biochemical, hematological, and metabolic changes in a cohort of 206 geriatric patients. The major strengths of this study are its relatively large sample size and its exclusive focus on the geriatric population. Significant increases were observed in serum urea and creatinine levels, accompanied by a significant decline in eGFR. In addition, FPG and glycated

hemoglobin (HbA1c) levels decreased markedly, TG levels declined, HDL cholesterol increased, and LDL as well as total cholesterol levels increased. Significant elevations were also observed in hemoglobin, RBC count, hematocrit, and platelet count. Notably, changes in eGFR, FPG, HbA1c, TGs, HDL cholesterol, total cholesterol, and LDL cholesterol were most pronounced during the first 3 months of treatment, after which the rate of change slowed, demonstrating a partial plateau between months 3 and 6. Although the clinical effects of SGLT2 inhibitors have been extensively investigated across various patient populations, studies specifically focusing on geriatric patients remain limited. Our findings provide a comprehensive characterization of the biochemical and clinical effects of SGLT2 inhibitors in older adults and contribute to the growing body of evidence supporting the importance of close metabolic, hematological, and renal monitoring during the early phase of treatment in this vulnerable population.

The most notable strengths of the study are its focus on the geriatric population and its large sample size; this has enabled a detailed assessment of the clinical, biochemical, and hematological effects of SGLT2 inhibitors in elderly individuals. Furthermore, the comprehensive measurement of parameters and the 6-month follow-up period represent a significant distinction from similar single-center, short-term studies in the literature.

Limitations

The study has certain limitations. The failure to directly measure volume and cardiovascular parameters limits a more comprehensive assessment of clinical effects in the geriatric population. The retrospective design, coupled with limitations in data collection and record-keeping, may result in some parameters being missing or non-standardized. No patients were excluded specifically because of unforeseen electrolyte imbalances or clinical conditions requiring treatment modification; however, such events may have influenced treatment continuity and follow-up in routine clinical practice and therefore cannot be completely excluded as potential sources of bias. In addition, there was a notable imbalance between the dapagliflozin and empagliflozin subgroups, with 190 and 16 patients, respectively. Therefore, drug-specific differences could not be adequately assessed, particularly because of the small number of patients in the empagliflozin subgroup. Furthermore, as the follow-up period is limited to just 6 months, it is not possible to establish the long-term efficacy and safety profile of SGLT2 inhibitors.

CONCLUSION

This study is one of the few to comprehensively demonstrate the effects of SGLT2 inhibitors on biochemical, hematological, metabolic, and hemodynamic parameters in the geriatric population. The findings indicate both significant changes in the early stages and a plateau effect in certain parameters, particularly regarding renal function, glycemic control, lipid profile, hematological parameters, and volume-related parameters. These results emphasize the need for careful monitoring and personalized follow-up when using SGLT2 inhibitors in geriatric patients. In clinical practice, these findings support closer monitoring during the initial treatment period, with dose titration and ongoing treatment decisions

individualized according to renal function, glycemic status, volume-related parameters, and overall clinical condition.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Researches Ethics Committee of Kırıkkale University (Date: 27.11.2024, Decision No: 2024.11.20).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: AH, AÇ, ZNÖ, AV, ŞÇ; Design: AH, AÇ, ZNÖ, AV, ŞÇ; Control: AH, AÇ, ZNÖ, AV, ŞÇ; Data Collection and/or Processing: AH; Analysis and/or Interpretation: AH, AÇ, ZNÖ, AV, ŞÇ; Literature Review: AH; Article Writing: AH, AÇ; Critical Review: AH, AÇ.

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Knowledge, attitudes, and practices of medical students regarding adult immunization: a cross-sectional study^a

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ABSTRACT

Aims: Our aim was to conduct a comparative assessment of medical students' knowledge, attitudes, and behaviors regarding adult vaccination by class year.

Methods: In a cross-sectional study conducted from January to May 2017 among medical students at a medical school, sociodemographic characteristics, knowledge levels regarding adult vaccines, and support for vaccination programs were assessed using a structured questionnaire. Knowledge scores were compared across class years; following univariate analyses of variables associated with support for vaccination programs, a binary logistic regression model was constructed.

Results: In our study, the rate of awareness of the Adult Immunization Guidelines was found to be significantly higher among sixth-year students ($p < 0.001$). In particular, the tendency to get vaccinated against hepatitis B and tetanus was also significantly higher among sixth-year students ($p < 0.001$). In a logistic regression analysis in which support for vaccination programs was taken as the dependent variable, it was found that a 1-unit increase in the score for skepticism regarding the necessity of vaccines reduced the likelihood of supporting vaccination programs by 55% (odds ratio (OR)=0.45), while an increase in the score for reluctance to get vaccinated reduced the likelihood of support by 38% (OR=0.62). It was found that a 1-unit increase in the belief that vaccinating adults is protective increased the likelihood of supporting vaccination programs by 3.70 times (OR=3.70), while an increase in the regular exercise score increased this likelihood by 1.54 times (OR=1.54) and an increase in the healthy eating score increased it by 1.81 times (OR=1.81).

Conclusion: Although it is observed that medical students' fundamental knowledge regarding adult immunization increases as the academic term progresses, their sense of being inadequately prepared in this area is likely to negatively affect their future ability to recommend vaccinations. Therefore, there is a need for structured educational interventions to raise awareness of adult immunization guidelines.

Keywords: Medical education, medical students, adult, immunization

^aA preliminary version of this study was presented as a poster presentation at the 16th International Eastern Mediterranean Family Medicine Congress in May 2017.

INTRODUCTION

Vaccination is among the most effective and cost-effective public health interventions for controlling infectious diseases and reducing mortality and morbidity. Vaccines administered in adulthood make a significant contribution to preventing serious infections, hospitalizations, and deaths. College students and students in the health sciences are both susceptible to infections and constitute a key group that can influence vaccination behavior in the community, due to their active social lives, their presence in crowded settings, and their potential to serve as role models for their peers.¹⁻³

Healthcare professionals and students are of particular importance both in terms of their own vaccination status and their approach to providing recommendations to patients. Medical students, as the doctors of the future, will play a decisive role in the planning, implementation, and counseling processes of adult vaccination programs after graduation. However, current findings indicate that even among

physicians and students, there may be gaps in knowledge regarding certain vaccines, misunderstandings or gaps in the understanding of guidelines, and hesitation or reservations about vaccines.⁴⁻⁷

The primary objective of this study is to examine medical students' knowledge and attitudes regarding adult immunization. In this context, assessing medical students' knowledge, attitudes, and behaviors regarding adult immunization is of critical importance for identifying gaps in current educational programs, developing targeted curricula and educational strategies, and ensuring that future physicians play an active role in adult immunization services. Given the goals of ensuring the success of national immunization programs and increasing adult vaccination rates, assessing medical students' level of preparedness regarding adult immunization is a critical requirement for both medical education and public health policies.^{1,2,8-10}

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METHODS

Ethics

This study was approved by the Clinical Researches Ethics Committee of Ondokuz Mayıs University (Date: 01.12.2016, Decision No: OMÜ KAEK 2016/362). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

The study was conducted using a cross-sectional and descriptive design among students at the Ondokuz Mayıs University School of Medicine.

Study Population and Sample Size

The study population consisted of 800 students in first-, second-, third-, and sixth-year at the Ondokuz Mayıs University School of Medicine during the 2016–2017 academic year. Only students who completed the family medicine internship were included in the study population; fourth- and fifth-year students who did not undertake this internship were excluded. The sample size was determined to be 260 participants using the OpenEpi 3.01 program, based on a 95% confidence level and a 5% margin of error. The study included students who voluntarily agreed to participate and provided informed consent. A total of 499 students participated in the study, which was conducted from January to May 2017.

Procedures and Data Collection

After reviewing previous national and international studies on the subject, a 73-question survey was administered to investigate medical students' knowledge, perceptions, and attitudes regarding adult immunization, as well as their sociodemographic characteristics, vaccination status, and levels of knowledge and attitudes toward vaccines. The survey was administered in person to students in first- to third-year students prior to their vocational skills laboratory courses, and sixth year students during their family medicine rotations.

Statistical Analysis

The research data were imported into a computer system and analyzed using "Statistical Package for Social Sciences (SPSS) for Windows 22.0 (SPSS Inc., Chicago, IL, USA)." Descriptive statistics were presented as mean±standard deviation (minimum–maximum), frequency distribution, and percentages. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. For comparisons between groups, the Pearson Chi-square test and Fisher's exact test were used for categorical variables, and for comparisons of group means, the independent samples t-test was used when the data followed a normal distribution. The Mann-Whitney U test was used for a nonparametric between-groups analysis to compare scores for attitudes, knowledge, and healthy lifestyle behaviors. Multivariate logistic regression analysis was conducted to identify the independent variables influencing participants' support for the vaccination program. Variables found to be statistically significant in univariate analyses or considered clinically or theoretically significant were included in the model. The findings were presented with adjusted odds ratio (OR) and 95% confidence intervals (CI). The values used in the model included the Hosmer–Lemeshow

test, multicollinearity check, Nagelkerke R^2 , and VIF values. Statistical significance was set at $p < 0.05$.

RESULTS

Medical students' knowledge, attitudes, and behaviors regarding adult immunization showed significant differences across years. The gender distribution was similar across years ($p = 0.910$) (Table 1). The 'Year' variable, presented in Table 1 of our study, represents the age distribution of the cases.

Table 1. Distribution of participants' descriptive and behavioral characteristics

Variables	1 st -3 rd years, n (%) (n=399)	6 th year, n (%) (n=100)	P
Gender			
Female	206 (51.6)	51 (51.0)	0.910
Male	193 (48.4)	49 (49.0)	
Year, (mean±SD (median) (min-max)	19.7±1.3	24.3±1.2	<0.001
Are you familiar with the adult immunization guidelines in our country?			
Yes	59 (16.0)	39 (42.4)	<0.001
No	113 (30.7)	17 (18.5)	
Undecided	196 (53.3)	36 (39.1)	
I'll get the flu shot.			
No	263 (65.9)	71 (71.0)	0.334
Yes	136 (34.1)	29 (29.0)	
I'll get the hepatitis B vaccine.			
No	133 (33.3)	11 (11.0)	<0.001
Yes	266 (66.7)	89 (89.0)	
I'll get the pneumococcal vaccine.			
No	264 (66.2)	65 (65.0)	0.826
Yes	135 (33.8)	35 (35.0)	
I'll get the tetanus vaccine.			
No	127 (31.8)	14 (14.0)	<0.001
Yes	272 (68.2)	86 (86.0)	
I'll get the HPV vaccine.			
No	250 (62.7)	63 (63.0)	0.949
Yes	149 (37.3)	37 (37.0)	
I think I'm healthy.			
I disagree	49 (12.3)	7 (7.0)	0.432
Undecided	68 (17.1)	15 (15.2)	
I agree	280 (70.6)	77 (77.7)	
I support vaccination programs.			
No	28 (8.9)	7 (8.1)	0.827
Yes	287 (91.1)	79 (91.9)	
I think there is a lack of information regarding adult immunization			
I disagree	33 (8.3)	15 (15.0)	0.108
Undecided	90 (22.6)	26 (26.0)	
I agree	275 (69.1)	59 (59.0)	
HPV: Human papillomavirus, SD: Standard deviation, Min: Minimum, Max: Maximum			

HPV: Human papillomavirus, SD: Standard deviation, Min: Minimum, Max: Maximum

The rate of awareness of the adult immunization guidelines in our country was 16.0% among students in years 1–3, but rose to 42.4% in year 6, and this increase was found to be statistically significant ($p < 0.001$). There was a significant increase in the tendency to get vaccinated, particularly for the hepatitis B vaccine (1st–3rd years: 66.7%; 6th year: 89.0%;

$p < 0.001$) and the tetanus vaccine (1st–3rd years: 68.2%; 6th year: 86.0%; $p < 0.001$). However, the proportion of students who indicated that they believed knowledge regarding adult immunization was insufficient remained high in both years; specifically, the proportion of those who agreed was 69.1% in 1st–3rd years and 59.0% in 6th year (Table 1).

For most statements—particularly regarding the *Haemophilus influenzae* type b (Hib) vaccine, the recommendation for adult Td/Tdap booster shots, the long-term protection provided by the hepatitis B vaccine, and pregnancy following the varicella vaccine—information scores were found to increase from the 1st–3rd years to the 6th year. A significant decrease in scores for incorrect statements—such as “The measles-mumps-rubella (MMR) vaccine is safe for use in pregnant women” and “Those

who receive the human papillomavirus (HPV) vaccine do not need cervical cancer screening”—in later stages indicates that students become better able to distinguish misinformation over time. The absence of a significant difference between cohorts in statements regarding pet bites, pneumococcal vaccine boosters, and the HPV vaccination schedule suggests that knowledge on these topics has increased only slightly, or that students already possessed a relatively good or moderate level of knowledge on these topics from the outset. As students advance to higher grades, there is a significant improvement in their understanding of basic and critical information regarding adult immunization; however, the increase in knowledge regarding certain specific or detailed topics remains more limited (Table 2).

Table 2. Participants' knowledge levels regarding vaccines

Proposition	First-year medical student mean (min–max)	Second-year medical student mean (min–max)	Third-year medical student mean (min–max)	Sixth-year medical student mean (min–max)	p
The <i>Haemophilus influenzae</i> type b (Hib) vaccine should be administered to individuals with functional or anatomical asplenia, immunoglobulin deficiencies, complement deficiency, or those undergoing chemotherapy or radiation therapy for malignancy following a stem cell transplant.	2.99 (1–5)	2.93 (1–5)	3.54 (1–5)	3.61 (1–5)	<0.001
Bites from domestic animals such as cattle, sheep, goats, horses, and donkeys are not considered a risk for rabies transmission.	2.88 (1–5)	2.75 (1–5)	2.70 (1–5)	2.87 (1–5)	0.539
For adult immunization, a tetanus-diphtheria (Td) booster is recommended every 10 years, including at least one dose of the diphtheria, tetanus, and acellular pertussis (Tdap) vaccine.	3.12 (1–5)	3.10 (1–5)	3.88 (1–5)	3.82 (1–5)	<0.001
The seasonal flu vaccine can be administered to children older than 2 months.	2.89 (1–5)	2.56 (1–5)	2.92 (1–5)	2.71 (1–5)	0.007
Recombinant flu vaccines can be safely administered to people with egg allergies.	2.87 (1–5)	2.76 (1–5)	2.70 (1–5)	2.47 (1–5)	0.005
Polysaccharide pneumococcal vaccines can be administered up to three times, with an interval of at least 5 years between doses, in accordance with the recommended schedules.	2.97 (1–5)	2.90 (1–5)	3.11 (1–5)	3.11 (1–5)	0.031
In the hepatitis B vaccination series, an anti-HBs level of ≥ 10 mIU/ml after the third dose provides long-term protection.	3.03 (1–5)	2.94 (1–5)	3.44 (1–5)	3.82 (1–5)	<0.001
Women who may become pregnant within 4 weeks of receiving the chickenpox vaccine should not be vaccinated.	3.25 (1–5)	3.11 (1–5)	3.66 (1–5)	3.96 (1–5)	<0.001
The herpes zoster (shingles) vaccine should be recommended.	3.03 (1–5)	2.93 (1–5)	3.23 (1–5)	2.92 (1–5)	0.013
The measles-mumps-rubella (MMR) vaccine can be safely administered to pregnant women.	3.02 (1–5)	2.79 (1–5)	1.97 (1–5)	1.86 (1–5)	<0.001
The HPV vaccine administered to girls aged 9–13 is the most cost-effective method for preventing cervical cancer.	3.05 (1–5)	3.10 (1–5)	3.52 (1–5)	3.21 (1–5)	<0.001
The vaccination schedule must be completed before engaging in sexual activity.	3.40 (1–5)	3.14 (1–5)	3.55 (1–5)	3.31 (1–5)	0.007
Women who have received the HPV vaccine do not need to undergo cervical cancer screening.	2.81 (1–5)	2.64 (1–5)	1.91 (1–5)	2.12 (1–5)	<0.001
The HPV vaccination schedule consists of 3 doses administered at 0, 2, and 6 months.	3.00 (1–5)	3.03 (1–5)	3.31 (1–5)	3.13 (1–5)	0.009

HPV: Human papillomavirus, Min: Minimum, Max: Maximum

“Yes” responses regarding vaccines that can be used in adult immunization were compared among medical students in their 1st–3rd years and 6th year. According to the results of the statistical analysis, reports regarding Hepatitis A ($p < 0.001$), Influenza ($p < 0.001$), HPV ($p = 0.004$), Herpes Zoster ($p = 0.009$), Pneumococcal ($p = 0.017$), Meningococcal ($p = 0.018$), and Hepatitis B ($p = 0.032$) vaccines, a statistically significant increase was observed in favor of 6th-year students. However, no statistically significant difference was observed between the two groups in the rates of vaccination for varicella ($p = 0.903$),

rabies ($p = 0.910$), Tdap ($p = 0.940$), Hib ($p = 0.506$), and MMR ($p = 0.58$) vaccines (Figure 1).

The scores for attitudes, knowledge, and behaviors related to a healthy lifestyle among medical students participating in the study were compared. No statistically significant difference was found between the students in terms of attitude scores ($p = 0.257$) and knowledge scores ($p = 0.314$). It was observed that attitude scores were concentrated at high levels in both groups, while knowledge scores clustered within a similar distribution range (centered around 3 points). An analysis

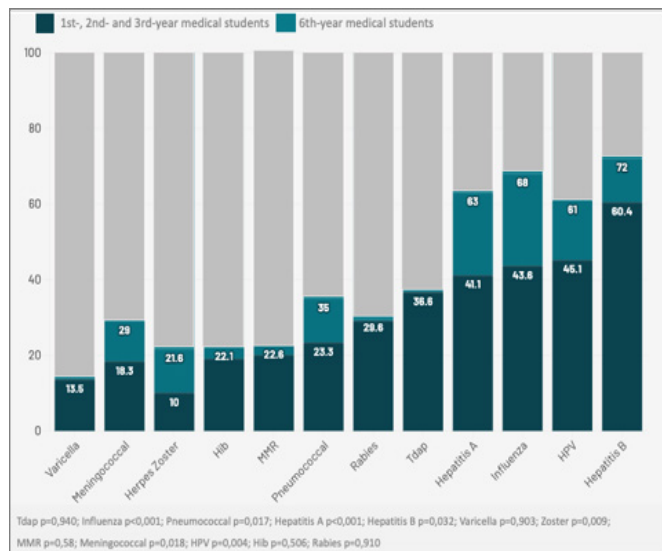


Figure 1. Comparison of “yes” responses regarding vaccines usable in adult immunization among students. Hib: *Haemophilus influenzae* type b, MMR: Measles-mumps-rubella, HPV: Human papillomavirus

of students’ healthy lifestyle behavior scores revealed a statistically significant difference between the 1st–3rd years and 6th year groups ($p < 0.001$) (Figure 2).

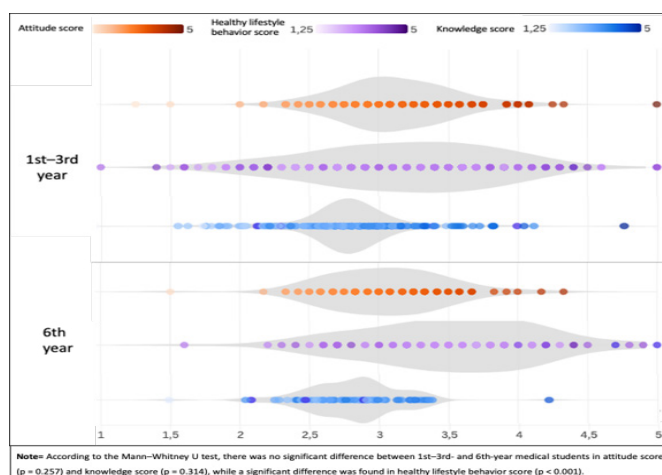


Figure 2. Distribution of knowledge, attitude, and healthy lifestyle behavior scores among 1st–3rd- and 6th-year medical students

A binary logistic regression model was constructed using the enter method with certain independent variables that were found to be significant ($p < 0.05$) in univariate analyses, as well as those that were not significant but had p -values below 0.20. A total of 366 individuals were included in the analysis due to missing data, and 6 outliers were excluded. The dependent variable is support for vaccination programs. A 1-unit increase in the score for skepticism regarding the necessity of vaccines reduces the likelihood of supporting vaccination programs by 55.4% (OR=0.45, 95% CI=0.24–0.83). An increase in the score for reluctance to get vaccinated also reduces the likelihood of support by 38% (OR=0.61, 95% CI=0.40–0.93). A 1-unit increase in the belief that vaccinating adults is protective was associated with a 3.70-fold increase in the likelihood of supporting vaccination programs (OR=3.70, 95% CI=1.89–7.25), an increase in the score for regular exercise increases the likelihood by 1.54 times (OR=1.54, 95% CI=1.08–2.20), and an increase in the score for healthy eating increases the likelihood by 1.81 times (OR=1.81, 95% CI=1.10–2.99) (Table 3).

DISCUSSION

Although the percentage of sixth-year medical students who are aware of the national vaccination guidelines has increased, a significant portion of students believe their knowledge of adult immunization is insufficient. The fact that more than half of these future physicians—who will graduate and be prescribing medications and administering vaccines to patients—feel insecure about this topic serves as the most striking warning sign that the “adult immunization” component of the medical school curriculum needs to be reviewed. In this study, the examination of medical students’ knowledge, attitudes, and behaviors regarding adult immunization is largely consistent with findings in the national and international literature on health students’ readiness regarding vaccination. Numerous studies have highlighted that the level of knowledge about vaccines among students in medicine, nursing, and other health-related fields is mostly moderate or inadequate, and that knowledge gaps are frequently observed, particularly regarding certain adult vaccines (HPV, influenza, hepatitis B, meningitis, etc.).^{1-4,11,12} Studies on HPV conducted in Brazil and India have shown that a lack of knowledge is more pronounced among male students in the early grades and

Table 3. Logistic regression analysis of factors associated with supporting vaccination programs among participants

Variables	β	Standard error	Wald	df	p	OR (95% CI)
I have my doubts about the necessity of vaccines.	-0.808	0.317	6.495	1	0.011	0.446 (0.24–0.83)
The views of people who serve as role models in society influence my decision on the issue of vaccination.	-0.358	0.242	2.177	1	0.140	0.699 (0.44–1.13)
Vaccinating adults is a method of protection.	1.309	0.343	14.598	1	<0.001	3.703 (1.89–7.25)
It is important to improve vaccination rates.	0.262	0.285	0.844	1	0.358	1.300 (0.74–2.27)
It is important for all adults to be fully vaccinated.	-0.070	0.284	0.061	1	0.805	0.932 (0.53–1.63)
I have my doubts about the effectiveness of vaccines.	-0.039	0.332	0.014	1	0.906	0.961 (0.50–1.84)
I exercise regularly.	0.434	0.181	5.733	1	0.017	1.543 (1.08–2.20)
I eat a healthy diet.	0.594	0.257	5.353	1	0.021	1.811 (1.10–2.99)
I wash my hands frequently.	0.588	0.305	3.719	1	0.054	1.801 (0.99–3.28)
I don't like getting vaccinated.	-0.491	0.215	5.208	1	0.022	0.61 (0.40–0.93)
Just as there is a vaccination program for childhood, there should also be one for adulthood.	0.386	0.271	2.036	1	0.154	1.472 (0.87–2.50)
Year	-0.145	0.120	1.455	1	0.228	0.865 (0.68–1.10)

*Overall percentage=93.7%, Nagelkerke R Square=0.470, Hosmer and Lemeshow p value=0.897. df: degrees of freedom, OR: Odds ratio, CI: Confidence interval

among those who have not been vaccinated, and that students do not acquire a complete understanding of key concepts (indications, special populations, use during pregnancy, and HIV-positive individuals) by the time they graduate.^{4,12} Similarly, for hepatitis B, a disconnect between knowledge and practice among health students has been reported; despite high levels of knowledge, full-course vaccination rates remain quite low.¹¹

The findings of our study indicate that students' attitudes toward adult vaccinations are generally positive, but the rate at which these attitudes translate into behavior is limited; this aligns with the phenomenon described in the literature as the "knowledge–attitude–behavior gap." It has been shown that acceptance and intention rates for COVID-19, influenza, and HPV vaccines are significantly higher among both nursing and medical students than actual vaccination rates; safety and side-effect concerns, "perceiving the risk of contracting the disease as low," cost and access issues, and institutional organizational shortcomings have been identified as barriers to vaccination.^{1,6,11–14} A meta-analysis of university students found that the intention to get routine vaccinations was around 54% for HPV and 43% for the flu, but that this intention was often hindered by contextual factors such as cost and availability.²

While awareness of the adult immunization guidelines published in our country is quite low among students in 1st–3rd years, it has increased significantly among 6th year students, though it has not yet reached an adequate level. In addition, a large proportion of students consider their knowledge of adult immunization to be insufficient. Lack of familiarity with the guidelines has led students to provide correct answers at a lower-than-expected rate to questions about which vaccines are recommended for adults. In knowledge-assessment questions on adult immunization administered to medical students, it was observed that 6th-year students scored higher on many vaccines, although the overall averages remained low. This finding suggests that greater exposure to adult immunization during clinical training and the opportunity to observe vaccine indications in practice contribute positively to students' knowledge levels.

It is an expected finding that the differences in knowledge and attitudes identified in our study are associated with variables such as gender, grade level, and subject area. Numerous studies have reported that female students have a higher level of knowledge on reproductive health topics such as HPV and family planning, whereas male students may be associated with both a knowledge gap and lower vaccine acceptance.^{1,4,12,15} The observation that both knowledge and vaccination behavior increase positively as the grade level rises reflects the impact of education on infectious diseases and public health provided prior to graduation; however, some studies have also shown that graduation does not guarantee an increase in knowledge on certain subtopics.⁴ This situation underscores the need to structure the curriculum specifically for adult immunization and to clearly define and assess core competencies based on current guidelines.^{8,10}

The fact that students exhibit hesitant or divided attitudes toward mandatory vaccinations—particularly those against highly contagious diseases—is consistent with the literature on vaccine hesitancy. A mixed-methods study conducted

among medical students in Germany showed that while there is greater support for mandatory vaccination against highly contagious diseases such as measles and COVID-19, mandatory vaccination is less widely accepted for diseases perceived as less serious.¹⁶ These findings indicate that medical students need educational activities that address not only biomedical knowledge but also the ethical, legal, and health policy dimensions.

Attitudes toward supporting vaccination programs are strongly associated with vaccine skepticism and beliefs about healthy living. The data show that beliefs and attitudes are the most important determinants of support for vaccination programs. A 1-unit increase in the vaccine necessity doubt score reduces support by approximately 55% (OR≈0.45), which is consistent with the literature on "vaccine hesitancy"; as trust and the perceived necessity of vaccination decrease, the intention to get vaccinated and acceptance of the vaccine decline significantly.^{17–20} Similarly, the finding that an increase in the "reluctance to get vaccinated" score reduces support is consistent with studies showing that negative emotional attitudes are a strong barrier to intention.^{20–22} On the other hand, the fact that support increases by approximately 3.7 times for every 1-unit increase in the belief that adult vaccination is protective is consistent with findings indicating that the "perceived benefits of vaccination" are the primary determinant of intention.^{18–20} In areas such as COVID-19 and HPV, it has been shown that individuals with a high perception of the benefits of the disease and the vaccine are much more likely to embrace the vaccine and vaccination programs.^{18,19,23}

The fact that increases in scores for regular exercise and healthy eating boost support for the vaccination program by 1.5–1.8 times suggests that a general health-oriented lifestyle is associated with preventive health behaviors, including vaccination.^{24–26} Findings indicating that physical activity and healthy eating improve both the risk of infection and the immune response to vaccines support the notion that these behaviors stem from the same foundation of health awareness.^{25,26}

Our study has important implications for policy and education. First, identifying the knowledge, attitudes, and behavior profiles of medical students regarding adult immunization provides a foundation for targeted curriculum revisions. Systematic reviews show that case-based learning, simulations, role-playing, and video-based online training can significantly increase knowledge about vaccination, self-efficacy, and the ability to address vaccine hesitancy.^{8,10,16} Second, it has been reported that there is a positive correlation between healthcare students' own vaccination status and their tendency to recommend vaccines to patients in the future; students who trust vaccines and have been vaccinated themselves are more likely to strongly recommend them to their patients.^{1,11,13,27} For this reason, it is important for medical schools to establish structured programs (such as free vaccination campaigns, on-campus reminder and appointment systems, etc.) to ensure that students complete their basic adult vaccinations before beginning clinical practice, both to protect the students and to reinforce the role model effect.^{6,8,10,11}

Limitations

There are some limitations that should be taken into account when interpreting this study. One of the most significant limitations is that the data were collected in 2017, that is, before the COVID-19 pandemic, which had a profound impact worldwide. As is well known, the pandemic has led to a dramatic increase in anti-vaccine sentiment, vaccine hesitancy, and negative attitudes toward vaccines on a global scale (particularly due to manipulation on social media and misinformation). Therefore, it is clear that perceptions of vaccination among the general public and among healthcare workers have taken on a new dimension in the wake of the pandemic. However, this does not diminish the value or relevance of the findings of our study. A review of the current literature on medical students in the post-pandemic period reveals that, as medical education progresses, the level of theoretical knowledge regarding adult immunization increases; however, issues such as specific vaccination schedules, awareness of guidelines, and feelings of inadequacy among students nearing graduation persist to a similar extent. In other words, despite the global vaccine debates sparked by the COVID-19 pandemic, the chronic shortcomings in medical education curricula regarding adult immunization and students' knowledge and attitude patterns remain valid in the literature. In this context, our study serves as a fundamental reference point in highlighting the time-independent, structural issues within medical education dynamics; it reaffirms, even during crisis periods such as the pandemic, just how critical adult vaccination education in the medical curriculum is and how much it needs to be improved. Since the sample was limited to a single faculty, the generalizability of the results to all medical students is limited. The fact that differences between groups based on the gender variable were not examined in the design of the current study constitutes one of the primary limitations of the research.

CONCLUSION

In awareness campaigns regarding adult vaccination, it is important to address both the cognitive and behavioral dimensions together. Reducing vaccine hesitancy and strengthening the perception of vaccine effectiveness are fundamental strategies for increasing public trust in vaccination programs. Accordingly, medical education programs should be structured to place greater emphasis on adult immunization, and students should be provided with opportunities to gain awareness in this area at both the theoretical and clinical levels. This will enable future healthcare professionals to play a more active role in preventive healthcare and help increase adult vaccination rates.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of Ondokuz Mayıs University (Date: 01.12.2016, Decision No: OMÜ KAEK 2016/362)." All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: MT, FAAİ; Design: MT; Control: FAAİ; Data Collection and/or Processing: MT; Analysis and/or Interpretation: MT, FAAİ; Literature Review: MT; Article Writing: MT; Critical Review: FAAİ.

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Clinicopathological characteristics of gastric polyps in an *Helicobacter pylori*-endemic region: a real-world cohort study

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ABSTRACT

Aims: Gastric polyps represent a heterogeneous group of mucosal lesions influenced by inflammatory, environmental, and pharmacologic factors. The distribution of polyp subtypes varies geographically, particularly in regions with high *Helicobacter pylori* (Hp) prevalence, where inflammation-driven lesions predominate. This study aimed to evaluate the clinicopathological characteristics of gastric polyps and their association with Hp infection and proton pump inhibitor (PPI) use in a real-world cohort.

Methods: In this retrospective cross-sectional study, 8,659 patients who underwent esophagogastroduodenoscopy (EGD) between January 2023 and January 2024 were screened, and 109 patients with histopathologically confirmed gastric polyps were included. Demographic features, endoscopic findings, histopathological subtypes, Hp status, background mucosal pathology, and PPI use were analyzed.

Results: The overall prevalence of gastric polyps was 1.25%. The mean age was 61.4±12.2 years, with a female predominance (73.4%). Hyperplastic polyps were the most common subtype (71.6%), followed by adenomatous (14.7%) and fundic gland polyps (6.4%). Hp positivity was significantly associated with hyperplastic polyps (p=0.011), while adenomatous polyps were significantly associated with chronic active gastritis (CAG) (p=0.016). All fundic gland polyps occurred in patients with long-term PPI use and were strongly associated with Hp negativity (p<0.001). No fundic gland polyps were observed in patients with concurrent Hp infection or chronic atrophic gastritis.

Conclusion: Gastric polyp development reflects the underlying gastric microenvironment shaped by inflammatory and pharmacologic factors. In Hp-endemic regions, hyperplastic polyps predominate and are strongly associated with Hp, whereas fundic gland polyps constitute a distinct entity linked to long-term PPI use and a lower prevalence of Hp infection.

Keywords: *Helicobacter pylori*, polyps, stomach, proton pump inhibitors

INTRODUCTION

Proliferative lesions originating from the gastric mucosa or submucosa and projecting into the lumen are defined as gastric polyps.^{1,2} Gastric polyps are detected in approximately 0.8–6% of upper gastrointestinal endoscopic procedures and are frequently identified incidentally during gastroscopy.^{1,3} Although most polyps are asymptomatic, they may present with gastrointestinal bleeding, anemia, abdominal discomfort, or, rarely, gastric outlet obstruction.^{4,5}

The histopathological distribution of gastric polyps varies geographically and appears to be influenced by environmental factors, *Helicobacter pylori* (Hp) prevalence, and proton pump inhibitor (PPI) use.^{1,2,4,6,7} Hyperplastic polyps and adenomatous polyps constitute the majority of cases, whereas fundic gland polyps are more commonly observed in Western populations with lower Hp prevalence and widespread PPI use.^{1,6,7} In contrast, hyperplastic and adenomatous/neoplastic gastric polyps appear to be relatively more prevalent in regions with a higher prevalence of Hp infection.⁸

Hp plays a central role in gastric carcinogenesis through chronic inflammation, mucosal atrophy, intestinal metaplasia, and

epithelial proliferation. Persistent Hp-induced gastritis leads to alterations in gastric epithelial turnover and may contribute to the development of hyperplastic and adenomatous polyps.⁹ Moreover, Hp eradication has been associated with regression of certain hyperplastic polyps, suggesting a potential causal relationship.¹⁰

Despite numerous epidemiological studies, data regarding the clinicopathological characteristics of gastric polyps in Hp-prevalent regions remain limited, and the interaction between Hp infection and specific polyp subtypes has not been fully elucidated. Therefore, the present study aimed to evaluate the demographic features, anatomical distribution, histopathological characteristics of gastric polyps, and their association with Hp infection in our population.

METHODS

Ethics

This study was approved by the Ethics Committee of Ankara Training and Researches Hospital (Date: 26.03.2025, Decision

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No: E-25-456). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

This retrospective cross-sectional study was conducted at the Department of Gastroenterology, Ankara Training and Research Hospital, between January 2023 and January 2024. Due to the retrospective design and use of anonymized data, the requirement for informed consent for study participation was waived.

During the study period, 8,659 patients who underwent esophagogastroduodenoscopy (EGD) for various clinical indications were retrospectively screened. Among these, 109 patients with histopathologically confirmed gastric polyps were included in the study. Lesions considered as polyp precursor changes, such as isolated foveolar hyperplasia without true polyp formation, were excluded. Patients with incomplete medical records were also excluded.

Demographic characteristics, presenting symptoms, history of PPI use, Hp status, presence of chronic active gastritis (CAG), atrophic gastritis, intestinal metaplasia, polyp localization, number, diameter, and histopathological subtype were recorded from electronic medical records. PPI use was defined as regular use of a PPI for at least 1 year prior to endoscopy.

Endoscopic Procedure

All endoscopic procedures were performed after a minimum fasting period of 8 hours. Patients were monitored throughout the procedure, which was carried out under local oropharyngeal anesthesia using 10% lidocaine spray with supplemental oxygen support.

All detected gastric polyps were removed endoscopically. Depending on the size and morphology of the lesion, polypectomy was performed using biopsy forceps or snare excision with electrocautery. In cases of multiple polyps, the diameter of the largest lesion was recorded for analysis. No procedure-related complications were observed.

To assess the background gastric mucosa and evaluate the presence of Hp infection, multiple biopsies were obtained from at least one site each from the antrum and corpus in all patients.

Histopathological Evaluation

All biopsy and polypectomy specimens were fixed in formalin, embedded in paraffin, and evaluated by experienced gastrointestinal pathologists. Histopathological classification of gastric polyps was based on routine pathological evaluation using standard histologic criteria and categorized as fundic gland polyps, hyperplastic polyps, and adenomatous polyps.¹¹

Gastric mucosal biopsies were evaluated in accordance with the Updated Sydney System.¹² Chronic gastritis was defined by mononuclear inflammatory cell infiltration in the lamina propria. CAG was defined by the presence of neutrophilic infiltration in addition to chronic inflammatory changes. Atrophic gastritis was diagnosed based on the loss of appropriate gastric glands, with or without accompanying intestinal metaplasia. Intestinal metaplasia was identified by the presence of goblet cells replacing the native gastric

epithelium. Hp infection was assessed histopathologically in gastric mucosal biopsies obtained from both the antrum and corpus.

Statistical Analysis

The data analyses were performed using Statistical Package for the Social Sciences v. 21 software (IBM SPSS for Windows version 21, IBM Corporation, Armonk, NY, USA). All continuous variables with normal distribution were defined as mean $\pm$ standard deviation, and non-normally distributed variables as median (min-max) values. Categorical variables were stated as number (n) and percentage (%). The comparisons of independent continuous variables between hyperplastic polyp and other polyps were performed using the Independent Samples t-test. The Mann-Whitney U test was applied to compare independent continuous variables between adenomatous polyps, fundic polyps, and other polyps. A binary logistic regression model including Hp status, gender, and the Hp status $\times$ gender interaction term was performed to assess whether the association between Hp infection and hyperplastic polyps differed by gender. The relationships between categorical variables were analyzed using Chi-square analysis or Fisher's Exact test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Gastric polyps were identified in 109 of 8,659 upper gastrointestinal endoscopies performed during the one-year study period, yielding an overall prevalence of 1.25%. The study cohort comprised 80 (73.4%) females and 29 (26.6%) males, with a mean age of 61.4 ± 12.2 years. The mean polyp diameter was 9.4 ± 6.6 mm (range, 2-50 mm). Regarding anatomical localization, polyps were most frequently found in the antrum ($n=41$, 37.6%), followed by the corpus ($n=33$, 30.3%), cardia ($n=27$, 24.8%), and fundus ($n=8$, 7.3%). When the patients were separated into two groups as <60 years and ≥ 60 years, the highest frequency of polyps was in the group aged ≥ 60 years (64 polyps, 58.7%). The most common presenting complaint was dyspepsia ($n=66$, 60.5%), followed by abdominal pain ($n=18$, 16.5%), anemia ($n=14$, 12.8%), and gastrointestinal bleeding ($n=5$, 4.5%). The demographic and baseline characteristics of patients with gastric polyps are summarized in [Table 1](#).

In gender-based analyses, no statistically significant difference was observed between female and male patients in terms of polyp localization or histological subtype. Polyp localization did not differ significantly by gender ($p=0.652$). Hyperplastic polyps were observed in 75.0% of females and 62.1% of males ($p=0.186$). Adenomatous polyps were detected in 12.5% of females and 24.1% of males ($p=0.148$), while fundic gland polyps were detected in 7.5% of females and 3.4% of males ($p=0.672$). A binary logistic regression model including Hp status, gender, and the Hp status $\times$ gender interaction term was performed to evaluate whether the association between Hp infection and hyperplastic polyps differed by gender. The interaction term was not statistically significant ($p=0.659$), indicating no evidence that gender modified the association between Hp infection and hyperplastic polyp occurrence.

Histopathologically, hyperplastic polyps were the most common subtype (71.6%), followed by adenomatous polyps

Table 1. Demographic characteristics of gastric polyps

Polyp type	Age	Gender (F/M)	Size (mm)	Cardia	Fundus	Corpus	Antrum	Multiple	Polypectomy
Hyperplastic (n=78)	61.3±12.2	60/18	9.1±6.8	21 (26.9%)	5 (6.4%)	21 (26.9%)	31 (39.7%)	14 (17.9%)	59 (75.6%)
Adenomatous (n=16)	63.9±10.8	10/6	11.2±6.2	3 (18.8%)	-	5 (31.3%)	8 (50%)	2 (12.5%)	16 (100%)
Fundic (n=7)	52.1±12.0	6/1	6.9±2.6	1 (14.3%)	3 (42.9%)	3 (42.9%)	-	2 (28.6%)	5 (71.4%)
NET (n=4)	58.8±10.3	2/2	8.3±3.9	-	-	3 (75%)	1 (25%)	-	1* (25%)
Adenocarcinoma (n=2)	78-81	-/2	10-30	2 (100%)	-	-	-	1 (50%)	**
GIST (n=1)	78	1/-	10	-	-	1 (100%)	-	-	***
Hamartomatous (n=1)	61	1/-	10	-	-	-	1 (100%)	1 (100%)	1 (100%)

F: Female, M: Male, NET: Neuroendocrine tumor, GIST: Gastrointestinal stromal tumor *While gastric surgical procedure was performed in one patient after polypectomy, direct gastric surgical procedure was performed in three patients without polypectomy. ** Gastric surgical procedure was performed without polypectomy in two patients. *** Gastric surgical procedure was performed without polypectomy in one patient.

(14.7%) and fundic gland polyps (6.4%). A single polyp was detected in 89 patients (81.7%), while 20 patients (18.3%) had multiple (≥ 2) polyps. The characteristics of the cases with a single polyp and multiple polyps are given in [Table 2](#).

Table 2. Comparison of data of cases with single or multiple polyps

	Single (n=89)	Multiple (n=20)	p
Age	63 (27-85)	64.5 (45-85)	0.184
Gender (F/M)	65 (73%) / 24 (27%)	15 (75%) / 5 (25%)	0.857
Localization	33 (37.1%) Antrum 27 (30.3%) Corpus 23 (25.8%) Cardia 6 (6.7%) Fundus	8 (40%) Antrum 6 (30%) Corpus 4 (20%) Cardia 2 (10%) Fundus	0.919
Chronic active gastritis	30 (33.7%)	9 (45%)	0.341
Intestinal metaplasia	25 (28.1%)	3 (15%)	0.226
Hp presence	41 (46.1%)	8 (40%)	0.622

F: Female, M: Male, Hp: *Helicobacter pylori*

Although not statistically significant, multiple polyps were more frequent among patients with hyperplastic polyps (n=14, 17.9%). While no statistically significant difference was observed in age distribution between hyperplastic and adenomatous polyps and other polyp types, fundic gland polyps were significantly more prevalent among younger patients compared to other polyp subtypes (p=0.048).

Histopathological background findings revealed chronic gastritis in 55 patients (50.5%), CAG in 39 patients (35.8%), and chronic atrophic gastritis in 14 patients (12.8%). While all adenomatous polyps underwent polypectomy, 19 hyperplastic (24.4%) and 2 (28.6%) fundic polyps were followed up due to endoscopic biopsy results and small dimensions (<5 mm). Gastric surgical procedures were performed in two

adenocarcinomas, one gastrointestinal stromal tumor, and four neuroendocrine tumor cases.

A history of Hp infection was present in 49 patients (45%), while 25 patients (22.9%) had a history of PPI use for more than one year. The most common types of polyps and their association with Hp are shown in [Table 3](#). Hp positivity was significantly more frequent in patients with hyperplastic polyps compared to other histological subtypes (p=0.011). In contrast, the majority of adenomatous polyps (n=10, 62.5%) were detected in patients with CAG, demonstrating a statistically significant association (p=0.016). All patients with fundic gland polyps had a history of long-term PPI use. A strong association was observed between PPI use and fundic gland polyp development (p<0.001). Notably, none of the patients with fundic gland polyps had concomitant CAG (p=0.048) or Hp infection (p=0.016).

DISCUSSION

Gastric polyps represent a heterogeneous group of lesions arising from overlapping pathogenic pathways, including mucosal inflammation, atrophy and metaplasia, as well as pharmacologically induced epithelial changes. In this real-world cohort, our findings indicate that gastric polyps are not isolated entities but rather reflections of the underlying gastric microenvironment. Within this framework, Hp plays a central role by promoting epithelial proliferation, particularly in hyperplastic polyp formation, whereas CAG was more closely associated with adenomatous transformation in our cohort, and PPI-induced hypergastrinemia contributes to the development of fundic gland polyps in Hp-negative settings. Overall, our findings suggest that gastric polyps should be interpreted within a multidimensional pathogenic framework integrating inflammatory, structural, and iatrogenic factors.

Table 3. Characteristics of patients by type of gastric polyp

	Hyperplastic polyp (n=78)	Other type (n=31)	p	Adenomatous polyp (n=16)	Other type (n=93)	p	Fundic polyp (n=7)	Other type (n=102)	p
Age (year)	61.3 ± 12.2	61.9 ± 12.3	0.800	64 (42-83)	63 (27-85)	0.396	53 (37-69)	63 (27-85)	0.048
Gender (F)	60 (76.9%)	20 (64.5%)	0.186	10 (62.5%)	70 (75.3%)	0.359	6 (85.7%)	74 (72.5%)	0.672
Multiple	14 (17.9%)	6 (19.4%)	0.864	2 (12.5%)	18 (19.4%)	0.731	2 (28.6%)	18 (17.6%)	0.610
Size (mm)	9.0±6.8	10.3±6.2	0.376	10 (3-25)	8 (2-50)	0.119	6 (3-10)	9 (2-50)	0.293
Chronic active gastritis	29 (37.2%)	10 (32.3%)	0.629	10 (62.5%)	29 (31.2%)	0.016	0 (0%)	39 (38.2%)	0.048
Intestinal metaplasia	18 (23.1%)	10 (32.3%)	0.322	6 (37.5%)	22 (23.7%)	0.351	1 (14.3%)	27 (26.5%)	0.675
Hp presence	41 (52.6%)	8 (25.8%)	0.011	6 (37.5%)	43 (46.2%)	0.516	0	49 (48%)	0.016

Data are presented as mean±standard deviation, median (minimum–maximum), or \%(n) (%), as appropriate. p: P-value, F: Female, Hp: *Helicobacter pylori*

In this retrospective cohort of patients undergoing EGD, gastric polyps were identified in 1.25% of cases, a prevalence consistent with previously reported rates of 0.8%–7.7%.^{11,13} Hyperplastic polyps were the predominant subtype, followed by adenomatous and fundic gland polyps.^{8,14} This distribution aligns with data from regions with high Hp prevalence, where inflammation-driven mucosal alterations predominate. The high frequency of hyperplastic polyps in our cohort likely reflects sustained mucosal injury and regenerative activity associated with chronic gastritis. These lesions are generally considered reactive rather than truly neoplastic and are thought to arise in the setting of chronic mucosal injury, reflecting exaggerated foveolar epithelial repair, regeneration, and hyperproliferation.¹⁵ Consistent with this mechanism, we observed a significant association between Hp infection and hyperplastic polyps. Hp colonization induces CAG characterized by neutrophilic infiltration, oxidative stress, and sustained release of proinflammatory cytokines, including IL-1 β and TNF- α , which disrupt epithelial homeostasis and promote compensatory proliferation.^{16,17} Over time, this process leads to architectural distortion, foveolar hyperplasia, and polyp formation. Importantly, evidence from meta-analyses demonstrates regression of hyperplastic polyps following Hp eradication, supporting a causal relationship rather than a mere association.^{10,18} Accordingly, our findings further support current recommendations advocating Hp testing and eradication in patients with hyperplastic gastric polyps.

In our cohort, adenomatous polyps were significantly associated with CAG, whereas no significant associations were observed with intestinal metaplasia or Hp infection. Although gastric adenomas are traditionally linked to atrophic and metaplastic changes, our findings suggest that, in real-world settings, active inflammatory changes may also accompany these lesions.^{8,19} CAG is characterized by persistent epithelial injury, neutrophilic infiltration, and increased cellular turnover, which may promote a microenvironment conducive to dysplastic transformation.^{15,20} Ongoing epithelial injury and regeneration may promote cell proliferation and oxidative DNA damage within an inflammatory mucosal microenvironment, thereby facilitating neoplastic progression. In addition, inflammatory mediators and reactive oxygen species generated in inflamed gastric mucosa may further contribute to DNA damage and malignant transformation.²⁰ However, given the cross-sectional design of our study, this association should be interpreted cautiously and does not imply a direct causal relationship.

Fundic gland polyps were observed exclusively in patients with long-term PPI use, demonstrating a strong association, while none were associated with Hp infection. This distinct distribution suggests a pathophysiological mechanism fundamentally different from inflammation-driven polyp formation. Chronic acid suppression induced by PPI therapy leads to sustained hypergastrinemia, which exerts trophic effects on the oxyntic mucosa and is associated with characteristic histologic changes, including parietal cell protrusion and cystic dilatation of fundic glands.²¹ The absence of Hp infection in patients with fundic gland polyps is consistent with prior studies reporting an inverse relationship between Hp-associated gastritis and the development of these lesions.^{22,23} Hp-related gastritis, particularly when

accompanied by glandular atrophy, may reduce functional parietal cell mass and thereby attenuate gastrin-mediated trophic effects on the fundic mucosa, potentially limiting polyp formation.²⁴ These findings are in line with large observational and meta-analytic studies demonstrating an increased prevalence of fundic gland polyps with prolonged PPI exposure.^{23,25,26} Clinically, this underscores the importance of periodic reassessment of long-term PPI therapy, particularly in patients without clear indications.

A key strength of our study is its real-world design, capturing a heterogeneous patient population with varying degrees of inflammation and medication exposure. Unlike controlled trials or highly selected cohorts, our findings reflect the complex interplay of multiple factors simultaneously influencing gastric mucosal pathology. This heterogeneity likely explains the variability in polyp distribution and behavior reported across studies. A female predominance was observed in our cohort. However, gender-based analyses did not demonstrate statistically significant differences in polyp localization or histological subtype. In addition, the Hp status $\times$ gender interaction term was not statistically significant in the logistic regression model, suggesting that the association between Hp infection and hyperplastic polyp occurrence did not differ significantly between female and male patients. Therefore, the observed female predominance should be interpreted cautiously and may reflect selection or referral bias related to the retrospective, endoscopy-based, single-center design rather than a definite biological predisposition.

Limitations

There are several limitations to the present study. First, this was a retrospective, single-center study with a relatively small sample size; therefore, our findings should be interpreted as real-world regional observations rather than a global assessment. In addition, the number of male patients and some subgroup sizes were limited, restricting the reliability of gender-stratified analyses. These findings should therefore be confirmed in larger multicenter cohorts with prespecified gender-based analyses. Second, the number of patients with long-term PPI use was limited, and the exact duration of PPI exposure could not be determined. Finally, long-term follow-up data were not available; therefore, we could not evaluate whether gastric polyps regressed after Hp eradication.

CONCLUSION

As a result, gastric polyps represent a heterogeneous group of lesions whose development is strongly influenced by the balance between inflammatory (Hp-driven) and pharmacologic (PPI-induced) factors. In Hp-endemic populations, hyperplastic polyps predominate and are closely linked to chronic gastritis, whereas fundic gland polyps, on the other hand, represent a distinct entity associated with long-term acid suppression and Hp negativity. These findings emphasize that gastric polyps should not be evaluated in isolation but in the context of the underlying gastric mucosal environment, and that management strategies should be guided by the combined assessment of histopathological features, Hp status, and medication exposure.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Ankara Training and Researches Hospital (Date: 26.03.2025, Decision No: E-25-456).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: BC; Design: BC; Control: BC; Data Collection and/or Processing: BC, YHP; Analysis and/or Interpretation: BC, YHP; Literature Review: BC; Article Writing: BC; Critical Review: BC.

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Acute uric acid nephropathy during DA-EPOCH-R therapy in primary mediastinal large B-cell lymphoma

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Dear Editor,

Primary mediastinal large B-cell lymphoma (PMBCL) is an aggressive lymphoma subtype that predominantly affects young adults and is commonly treated with dose-adjusted EPOCH-R (DA-EPOCH-R), which provides high response and cure rates.^{1,2} Despite its efficacy, intensive chemotherapy regimens may lead to rare but clinically significant metabolic and renal complications. Here, we report a case of acute kidney injury (AKI) developing during DA-EPOCH-R therapy, suggestive of acute uric acid nephropathy, with concomitant acyclovir-associated nephrotoxicity remaining a possible contributing factor, in the absence of classical tumor lysis syndrome (TLS).

A 32-year-old male patient with PMBCL developed AKI on day +17 following initiation of the fourth cycle of DA-EPOCH-R (dose level 4, initiated on October 27, 2025). On November 13, 2025, serum creatinine increased to 5.79 mg/dl (KDIGO stage 3), accompanied by an elevated serum uric acid level of 9.4 mg/dl. The patient was hemodynamically stable, non-oliguric, and did not exhibit electrolyte abnormalities typically associated with TLS. Renal ultrasonography and Doppler studies excluded obstructive or vascular causes. Urine sediment analysis performed on November 14, 2025, revealed amorphous urate crystals, while acyclovir crystals were not detected despite being specifically sought. Notably, allopurinol prophylaxis had been discontinued prior to this episode due to previously normal uric acid levels and low perceived TLS risk. During follow-up, the patient had also been receiving intravenous acyclovir at therapeutic doses.

Based on clinical and laboratory findings, acute uric acid nephropathy was considered a possible cause of AKI, although concomitant acyclovir-associated nephrotoxicity could not be excluded. Intravenous hydration was intensified, and potentially nephrotoxic agents, particularly acyclovir, were discontinued on November 13, 2025, immediately after AKI was identified. Renal function gradually improved, with serum creatinine and uric acid levels returning near baseline

(Figure). However, the simultaneous initiation of hydration and discontinuation of acyclovir prevented definitive attribution of AKI to a single mechanism.

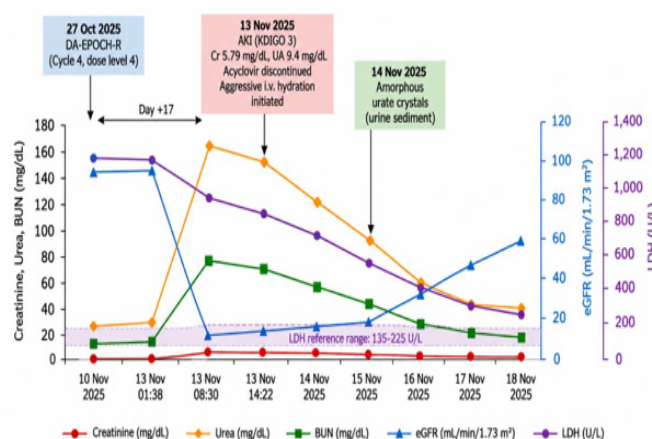


Figure. This figure shows the temporal changes in the patient's serum creatinine, urea, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), and lactate dehydrogenase (LDH) levels between November 10 and November 18, 2025. The fourth cycle of DA-EPOCH-R was initiated on October 27, 2025. Acute kidney injury and hyperuricemia were identified on November 13, 2025 (creatinine, 5.79 mg/dl; uric acid, 9.4 mg/dl), when intravenous acyclovir was discontinued and intensified hydration was initiated. Urine sediment examination on November 14, 2025, revealed amorphous urate crystals, while specifically sought acyclovir crystals were not detected. Renal parameters and LDH values are displayed on the same time axis, with separate axes used for eGFR and LDH. Reference range limits for LDH are indicated with dashed lines

Although TLS is a well-recognized cause of AKI in lymphoma patients receiving intensive chemotherapy, isolated acute uric acid nephropathy without classical TLS criteria has been reported, particularly in highly proliferative malignancies.^{3,4} According to the Cairo-Bishop classification, laboratory TLS requires at least two characteristic metabolic abnormalities within the defined period surrounding chemotherapy.⁴ Uric acid crystal precipitation in renal tubules may lead to intrarenal obstruction and subsequent AKI. In the present

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case, hyperuricemia and amorphous urate crystals supported the possibility of uric acid-associated nephropathy, although these findings were not diagnostic. Moreover, AKI developed outside the conventional Cairo–Bishop laboratory TLS time window. In addition, acyclovir-associated nephrotoxicity should be considered in the differential diagnosis, especially in the setting of intravenous administration and high doses.⁵⁻⁷ The absence of acyclovir crystals in urine sediment does not exclude this diagnosis, as crystal detection may be inconsistent. Acyclovir may also cause renal injury through mechanisms other than crystal precipitation. In the absence of renal biopsy, the relative contributions of uric acid-associated nephropathy and acyclovir-related nephrotoxicity could not be determined conclusively.

This case highlights that AKI during DA-EPOCH-R therapy may be multifactorial. Even in the absence of classical TLS findings, uric acid-associated nephropathy and drug-related nephrotoxicity should be considered. Early recognition, prompt discontinuation of nephrotoxic agents, and aggressive supportive management are critical to prevent irreversible renal damage.

In patients with PMBCL receiving intensive chemotherapy, AKI may develop independently of classical TLS criteria. Uric acid-associated nephropathy and concomitant drug-induced nephrotoxicity should be considered as potentially overlapping mechanisms, and early intervention may significantly improve outcomes.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient for the publication of this correspondence and any related clinical details.

Peer Review Process

This letter was externally peer-reviewed.

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Editor Note

Serhat Çelik is a member of the Editorial Board of this journal. He was not involved in the editor assignment, reviewer selection, peer review process, or editorial decision for this manuscript. The peer review process was managed independently by another editor.

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Reevaluating long-term proton pump inhibitor safety: potential metabolic drug interactions and personalized prescribing

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Dear Editor,

Proton pump inhibitors (PPIs) are widely used to treat acid-related disorders and prevent aspirin/NSAID-induced ulcers and are generally considered safe and clinically beneficial. However, their use has expanded to conditions for which their benefits are not fully established, potentially exposing patients to unnecessary risks. Although several adverse effects have been reported, their clinical significance remains uncertain because much of the evidence comes from retrospective observational studies with relatively low hazard ratios. Therefore, PPIs should be prescribed when clear clinical benefits are expected, and their long-term safety should be evaluated through high-quality prospective studies.¹

Although PPIs are unlikely to act as independent carcinogens, observational studies have reported an association between their use and gastrointestinal cancer, particularly gastric cancer; however, causality remains unproven. Proposed biological mechanisms include secondary hypergastrinemia, sustained elevation of gastric pH, alterations in the gastric microbiota, and enterochromaffin-like cell hyperplasia, which may theoretically contribute to gastric mucosal changes.² Supporting these concerns, a meta-analysis of 25 cohort studies found an approximately twofold increased risk of gastrointestinal cancer among PPI users, with increased risks reported for esophageal, gastric, liver, and pancreatic cancers, but not colorectal cancer. The association was also observed among individuals using PPIs for less than one year.³ However, these findings should be interpreted cautiously because of potential confounding, particularly from *Helicobacter pylori* infection, underlying gastrointestinal disease, and treatment indications. Overall, the available observational evidence does not establish a causal relationship between PPI use and cancer development.

Omeprazole (a PPI) can cause drug–drug interactions through inhibition of CYP2C19 and CYP3A4, with its metabolites also contributing to the overall interaction magnitude. Although the parent drug alone may be sufficient to identify some interaction risks, incorporating metabolite-mediated effects may improve quantitative predictions of clinical

drug–drug interactions. Importantly, metabolite exposure and lipophilicity alone do not reliably predict inhibitory contribution.⁴ Concomitant medications that inhibit or otherwise modify CYP2C19 and CYP3A4 activity may alter omeprazole metabolism and systemic exposure, particularly in patients receiving multiple medications. However, the magnitude and clinical significance of these effects depend on the specific medication and metabolic pathway involved. The extent to which concomitant CYP-modifying medications are characterized in drug safety and epidemiological studies should be assessed on a study-by-study basis rather than generalized across the literature. Future pharmacovigilance and epidemiological studies should systematically document concomitant CYP2C19- and CYP3A4-modifying medications to better characterize potential pharmacokinetic interactions and evaluate their implications for long-term safety outcomes. Although these interactions may be clinically relevant, their implications for long-term outcomes, particularly gastric cancer risk, remain uncertain. Direct evidence establishing that these interactions modify PPI-associated gastric cancer risk is currently insufficient; therefore, this proposed relationship should be considered hypothesis-generating.

Interindividual variability in PPI metabolism and treatment response related to CYP2C19 genetic polymorphisms is well documented. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published a guideline on CYP2C19 genotype-guided PPI dosing, including recommendations relevant to drug exposure and therapeutic efficacy.⁵ However, whether CYP2C19 genotype or concomitant CYP-modifying medications influence long-term gastric cancer risk remains unresolved. Future studies integrating genotype data, detailed medication histories, PPI exposure, and relevant confounders are needed to investigate this potential relationship.

Although observational studies have reported associations between PPI use and gastric cancer, current evidence does not establish a causal relationship. CYP2C19 variability and CYP-mediated drug interactions provide a pharmacological rationale for investigating differences in PPI exposure, but a

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direct link between genotype, concomitant CYP-modifying medications, and gastric cancer risk remains unproven. This should be regarded as a hypothesis-generating research question. Future prospective studies should incorporate detailed PPI exposure and indication, concomitant medication histories, CYP2C19 genotype, and relevant confounders—including *Helicobacter pylori* infection, age, and smoking—to determine whether these factors modify gastric cancer outcomes. Personalized PPI prescribing should continue to be guided by established clinical indications and evidence-based pharmacogenetic recommendations; biological plausibility alone is insufficient to infer cancer risk.

ETHICAL DECLARATIONS

Peer Review Process

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Author Contributions

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