https://doi.org/10.46389/rjd-2025-1840
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2025; volume 32, issue 1, pages 40–48

Original Article

# A prospective study on the relationship between comorbidities and metformin-induced gastrointestinal symptoms in elderly patients with diabetes

**Jeevanandham Sivakumar [1], Venkatesaprasath Ravichandran [1], Abinaya Paramanantham [1], Venkateswaramurthy Nallasamy [1] ***

[1] Department of Pharmacy Practice, JKKN College of Pharmacy, Kumarapalayam, Namakkal, Tamil Nadu, India

* Correspondence to: Venkateswaramurthy Nallasamy, Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam, Namakkal, Tamil Nadu, 638183, India. Phone: +91 98427 24689; E-mail: nvmurthi@gmail.com

Received: 22 December 2024 / Accepted: 25 February 2025

## Abstract

This study explores the impact of comorbidities on Metformin-induced gastrointestinal (GI) symptoms in elderly patients with Type 2 diabetes mellitus. Conducted over six months at a tertiary care hospital in Erode, India, the prospective study involved 200 patients aged 55 years and above. Participants were categorized into two groups—those with additional comorbidities [such as hypertension (HTN) and coronary artery disease (CAD)] and those without. Data collection utilized a structured 20-question questionnaire focusing on Metformin usage, GI symptoms, and comorbid conditions. The findings revealed that elderly patients with both Type 2 diabetes and HTN had a significantly higher incidence of GI symptoms (69.44%) compared to those with diabetes alone (54.16%) or HTN alone (56%). The highest prevalence of symptoms was observed in patients with diabetes, HTN, and CAD (70.83%). Abdominal pain emerged as the most common symptom, particularly among those concurrently taking Amlodipine, affecting 15 cases. Additionally, lifestyle factors like smoking and alcohol use further increased GI symptom prevalence, with smokers showing a rate of 91.6% and alcohol users 81.81%. These results underscore the exacerbating role of comorbid conditions like HTN and CAD on Metformin-induced GI symptoms in elderly patients, complicating diabetes management. The study highlights the need for careful assessment and tailored management strategies for this demographic to mitigate adverse effects and improve therapeutic outcomes.

**Keywords:** metformin, gastrointestinal symptoms, comorbidities, elderly patients, type 2 diabetes mellitus.

## Introduction

Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels and increased glycated hemoglobin (HbA1c), has reached epidemic proportions globally [1]. It is one of the leading causes of morbidity and mortality worldwide, with the prevalence steadily rising, particularly among the elderly population. Diabetes has a global prevalence of 8.8% in adults in 2017, with an estimated 48% increase to 628.6 million people by 2045 [2]. In elderly patients, comorbid conditions with diabetes include cardiovascular diseases, hypertension, chronic kidney disease, osteoarthritis, and cognitive decline. It is estimated that nearly 60% of elderly patients with diabetes have at least one additional chronic condition, and up to 40% may have four or more comorbidities [3–6]. Metformin, a biguanide, shows similar or better safety and efficacy than other treatments for managing type 2 diabetes in older adults, but the quality and quantity of evidence are low [7].

It achieves these effects by reducing the glucose production in the liver, enhancing the uptake of glucose in the periphery, and enhancing the sensitivity to

insulin. Despite its potency, metformin causes a variety of gastrointestinal adverse effects, which form one of the most frequently voiced complaints by diabetic patients [8]. For elderly patients who already suffer from compromised gastrointestinal function due to aging, these metformin-induced GI symptoms could become more pronounced and complicated to manage. Besides the direct gastrointestinal side effects, pharmacokinetic and pharmacodynamic alterations that come with age are some changes that complicate the use of metformin for therapy in old patients [9, 10].

With aging, the body undergoes various physiological changes that would alter drug absorption, distribution, metabolism, and excretion. Reduced renal clearance, which is common with elderly patients, can result in decreased clearance of metformin, leading to a higher chance of metformin accumulation in the body and possible adverse effects such as lactic acidosis, a rare but life-threatening side effect [11]. Besides, aging is linked with alterations in gastrointestinal motility, gastric acid secretion, and intestinal transit time that can alter the rate and extent of metformin absorption, thus affecting its efficacy and side effects. The impact of comorbid conditions on the incidence and severity of metformin-induced gastrointestinal symptoms has not yet been well studied [12]. Conducting research in this direction will be helpful in understanding how comorbid conditions such as hypertension, cardiovascular diseases, chronic kidney diseases, and gastrointestinal disorders would interact with metformin therapy.

The presence of cognitive impairments, such as dementia, in elderly diabetic patients, may impair the recognition and reporting of GI side effects, leading to underreporting and inappropriate management of these symptoms [13].

This study is intended to investigate the relationship between comorbidities and metformin-induced gastrointestinal symptoms in the elderly, aiming to fill the knowledge gap in this important area. By exploring how comorbid conditions of various kinds impact the severity and incidence of GI side effects, this study will advance personalized treatment strategies tailored to the health status of elderly diabetic patients. Such an approach is crucial in order to improve patient adherence to diabetes treatment, reduce healthcare costs, and improve overall well-being among this vulnerable population. The findings could, therefore, guide healthcare providers in decision-making about the management of diabetes in older adults while considering the benefits and risks of metformin therapy in the presence of comorbidities.

## Material and methods

### Study design and setting

This study was conducted at a Tertiary Care Hospital in Erode over a six-month period. The hospital was selected for its extensive experience in managing diabetic patients and its comprehensive medical records system, which provided an appropriate environment for this research. The study aimed to investigate the relationship between comorbidities and metformin-induced gastrointestinal (GI) symptoms in elderly patients with Type 2 diabetes mellitus. It had a cross-sectional design, which classified participants into two groups: a group of patients with Type 2 diabetes on metformin alone and another group of patients with Type 2 diabetes on metformin who also had one or more comorbid conditions, including hypertension and coronary artery disease (CAD).

### Sample size calculation

This study's sample size was determined using RaoSoft statistical software, with a margin of error of 5% and a 95% confidence interval. Using these parameters, the calculated sample size was 200 patients.

### Study population

The study consisted of patients aged 55 years and above, diagnosed with Type 2 diabetes mellitus, and who were currently receiving metformin therapy. The patients were divided into two groups:

Group 1: Patients with Type 2 diabetes on metformin monotherapy without any other comorbidities.

Group 2: Type 2 diabetes patients receiving metformin treatment, along with treatment for comorbidities such as hypertension and CAD. The study evaluated both groups in terms of gastrointestinal symptoms due to metformin intake, including symptom intensity. Common GI symptoms studied were abdominal pain, nausea, vomiting, bloating, and diarrhea, along with how they occurred with or without the presence of diabetes and comorbid conditions.

### Inclusion criteria

Participants were selected based on specific inclusion criteria to ensure the study's focus on the target population. The study included patients aged 55 years and older who were diagnosed with Type 2 diabetes

mellitus and were currently undergoing metformin therapy. Participants in Group 2 were required to have Type 2 diabetes and be managing one or more comorbidities, such as hypertension or coronary artery disease. Furthermore, patients had to be willing to participate in the study and capable of understanding and responding to the structured questionnaire.

### Exclusion criteria

The study excluded participants who did not meet the inclusion criteria and those with conditions that might confound the results. Individuals with Type 1 diabetes mellitus were excluded, as the focus was specifically on Type 2 diabetes. Patients not on metformin therapy were also excluded, as the study aimed to assess the impact of metformin on gastrointestinal symptoms. Those with pre-existing gastrointestinal disorders, such as inflammatory bowel disease, peptic ulcers, or other conditions that could influence GI symptoms, were also excluded.

### Data collection tool

A 20-question structured questionnaire was based on a Likert scale prepared for data collection. This questionnaire focused on metformin use, gastrointestinal symptoms, and comorbidities. Detailed questions about metformin usage, such as the dose administered, duration of treatment, and any dose adjustments, were part of the questionnaire. It also evaluated the degree, severity, and onset of gastrointestinal symptoms like abdominal pain, nausea, bloating, vomiting, and diarrhea. In addition, it asked whether the patients suffered from any other chronic conditions, including hypertension, coronary artery disease, or chronic kidney disease. It was validated with respect to relevance and accuracy through expert review in the fields of endocrinology, geriatrics, and pharmacology. The pilot study was undertaken to check for clarity, consistency, and comprehensibility; changes were implemented based on expert feedback for enhanced effectiveness.

### Statistical analysis

Once the data collection process was complete, the collected data were analyzed using software packages like SPSS or R. Descriptive statistics were used to summarize the demographic and clinical characteristics of participants. For comparisons between two groups, chi-square tests were applied for categorical variables and t-tests for continuous variables. A p-value of less than 0.05 was considered to be statistically significant. A multivariate analysis was carried out to understand the independent effects of comorbid conditions on the severity of gastrointestinal symptoms while controlling for age and gender.

## Results

### Impact of comorbidities on gastrointestinal symptoms

The study found that elderly patients with both Diabetes Mellitus (DM) and Hypertension (HTN) who were taking Metformin exhibited significantly higher rates of gastrointestinal (GI) symptoms (69.44%) compared to patients with only Diabetes Mellitus (54.16%) or only Hypertension (56%). Furthermore, patients with Coronary Artery Disease (CAD), Hypertension, and Diabetes Mellitus taking Metformin reported even higher GI symptom rates (70.83%) compared to those with only Diabetes Mellitus (54.16%). These findings highlight the increased risk of GI symptoms in patients with multiple comorbidities when combined with Metformin use (Table 1).

### Prevalence of specific gastrointestinal symptoms

Abdominal pain emerged as the most frequently reported symptom among all the antihypertensive drugs analyzed. It was most common in patients taking Amlodipine (15 cases), whereas patients on Atenolol reported the fewest cases (3 cases). Heartburn was also notably prevalent, especially in Amlodipine users (20 cases), compared to only one case in the Atenolol group. Bloating was more commonly reported among Amlodipine users (9 cases), with fewer occurrences in Atenolol and Enalapril users. Nausea and vomiting were significant symptoms, with Amlodipine users reporting 8 cases of nausea and 5 cases of vomiting. Enalapril users had 4 cases of nausea, while Furosemide users reported 3 cases of vomiting. These findings suggest that the type of antihypertensive medication may influence the frequency and nature of gastrointestinal symptoms in patients with Diabetes Mellitus (Table 2).

### Synergistic effects of comorbidities on GI symptoms

The study observed a heightened risk (15.28%) of gastrointestinal symptoms in patients with both Diabetes


https://doi.org/10.46389/rjd-2025-1840

Table 1: Comparison of gastrointestinal symptoms in patients with Diabetes Mellitus and hypertension taking Metformin, patients with hypertension alone, patients with coronary artery disease, hypertension, and Diabetes Mellitus taking Metformin, and patients with coronary artery disease alone.

| S.No | GI symptoms | Patients with DM taking Metformin (N=39) | Patients with DM and hypertension taking Metformin (N=25) | Patients with hypertension (N=14) | Patients with coronary artery disease, hypertension and DM taking Metformin (N=34) | Patients with coronary artery disease (N=33) |
|---|---|---|---|---|---|---|
| | **Patients with GI symptoms (N=129) Percentage (%)** | **39 (54.16%)** | **25 (69.44%)** | **14 (56%)** | **25 (75.75%)** | **26 (70.83%)** |
| **1.** | Abdominal Pain | 22 (56.4%) | 16 (64%) | 8 (57.14%) | 19 (73%) | 12 (48%) |
| **2.** | Epigastric pain | 15 (38.4%) | 11 (44%) | 6 (42.85%) | 11 (42.3%) | 11 (44%%) |
| **3.** | Heart burn | 22 (56.4%) | 16 (64%) | 8 (57.14%) | 14 (53.84%) | 15 (60.75%) |
| **4.** | Bloating | 10 (25.6%) | 7 (28%) | 5 (35.71%) | 4 (15.38%) | 8 (32%) |
| **5.** | Regurgitation | 3 (7.6%) | 4 (16%) | 1 (7.14%) | 2 (7.6%) | 8 (32%) |
| **6.** | Abdominal rumbling | 12 (30.7%) | 3 (12%) | 4 (28.57%) | 4 (15.38%) | 6 (24%) |
| **7.** | Empty feeling | 14 (35.8%) | 2 (8%) | 1 (7.14%) | 7 (26.92%) | 10 (40%) |
| **8.** | Nausea | 9 (23%) | 7 (28%) | 4 (28.57%) | 10 (38.46%) | 10 (40%) |
| **9.** | Vomiting | 7 (17.9%) | 7 (28%) | 6 (42.85%) | 13 (50%) | 11 (44%) |
| **10.** | Loss of Appetite | 6 (15.3%) | 3 (12%) | 3 (21.42%) | 7 (26.92%) | 9 (36%) |
| **11.** | Belching | 3 (7.6%) | 4 (16%) | 2 (14.28%) | 8 (30.76%) | 1 (4%) |
| **12.** | Hematemesis | 1 (2.5%) | 2 (8%) | 2 (14.28%) | 4 (15.38%) | 2 (8%) |
| **13.** | Flatulence | 0 (0%) | 1 (4%) | 1 (7.14%) | 5 (19.23%) | 3 (12%) |
| **14.** | Dysphagia | 2 (5.12%) | 0 (0%) | 1 (7.14%) | 3 (11.53%) | 2 (8%) |
| **15.** | Bloody stools | 8 (20.5%) | 0 (0%) | 1 (7.14%) | 2 (7.69%) | 6 (24%) |
| **16.** | Mucus stool | 1 (2.5%) | 1 (4%) | 0 (0%) | 8 (30.76%) | 3 (12%) |
| **17.** | Stools Frequent with pain | 3 (7.6%) | 1 (4%) | 1 (7.14%) | 4 (15.38%) | 3 (12%) |
| **18.** | Diarrhea | 1 (2.5%) | 5 (20%) | 5 (35.71%) | 6 (23.%) | 4 (16%) |
| **19.** | Constipation | 1 (2.5%) | 1 (4%) | 1 (7.14%) | 11 (42.3%) | 2 (8%) |
| **20.** | Frequent with Hard | 1 (2.5%) | 3 (12%) | 1 (7.14%) | 7 (26.92%) | 5 (20%) |

Mellitus and Hypertension taking Metformin. This may be attributed to the synergistic effects of these conditions, which can lead to systemic inflammation and altered gut motility. These physiological changes could exacerbate Metformin-induced GI side effects, emphasizing the complex interaction between metabolic disorders and drug responses.

## Impact of smoking and alcohol on GI symptoms

Among patients with both Diabetes Mellitus and Hypertension who were taking Metformin, smokers experienced a significantly higher rate of gastrointestinal symptoms (91.6%) compared to non-smokers (58.33%). Similarly, patients who drank alcohol had a

Table 2: Percentage of GI symptoms among patients taking different medications.

| S.No | GI symptoms | Aspirin | Clopidogrel | Atorvastatin | Furosemide | Spironolactone | Enalapril | Atenolol |
|---|---|---|---|---|---|---|---|---|
| 1. | Abdominal Pain | 76.92% | 80.00% | 82.61% | 75.00% | 100.00% | 84.21% | 80.00% |
| 2. | Epigastric pain | 73.33% | 81.82% | 84.61% | 25.00% | 33.33% | 83.33% | 66.67% |
| 3. | Heart burn | 100.00% | 85.71% | 76.47% | 25.00% | 100.00% | 78.57% | 75.00% |
| 4. | Bloating | 100.00% | 75.00% | 100.00% | 25.00% | 100.00% | 0.00% | 0.00% |
| 5. | Regurgitation | 71.43% | 100.00% | 100.00% | 0.00% | 0.00% | 50.00% | 50.00% |
| 6. | Abdominal rumbling | 100.00% | 100.00% | 100.00% | 25.00% | 0.00% | 85.71% | 100.00% |
| 7. | Empty feeling | 85.71% | 100.00% | 100.00% | 0.00% | 100.00% | 0.00% | 100.00% |
| 8. | Nausea | 85.71% | 75.00% | 100.00% | 25.00% | 0.00% | 57.14% | 60.00% |
| 9. | Vomiting | 71.43% | 88.89% | 88.89% | 84.62% | 66.67% | 71.43% | 75.00% |
| 10. | Loss of Appetite | 100.00% | 83.33% | 100.00% | 25.00% | 66.67% | 100.00% | 75.00% |
| 11. | Belching | 100.00% | 100.00% | 100.00% | 0.00% | 100.00% | 83.33% | 100.00% |
| 12. | Hematemesis | 100.00% | 100.00% | 100.00% | 0.00% | 0.00% | 100.00% | 0.00% |
| 13. | Flatulence | 100.00% | 50.00% | 75.00% | 25.00% | 100.00% | 75.00% | 50.00% |
| 14. | Dysphagia | 100.00% | 100.00% | 100.00% | 0.00% | 0.00% | 100.00% | 100.00% |
| 15. | Bloody stools | 100.00% | 100.00% | 100.00% | 0.00% | 0.00% | 100.00% | 0.00% |
| 16. | Mucus stool | 100.00% | 100.00% | 100.00% | 0.00% | 0.00% | 85.71% | 100.00% |
| 17. | Stools Frequent with pain | 100.00% | 100.00% | 100.00% | 0.00% | 100.00% | 25.00% | 0.00% |
| 18. | Diarrhea | 85.71% | 100.00% | 100.00% | 0 | 0 | 100.00% | 100.00% |
| 19. | Constipation | 77.78% | 100.00% | 100.00% | 25.00% | 0.00% | 100.00% | 100.00% |
| 20. | Frequent with Hard | 85.71% | 100.00% | 100.00% | 0.00% | 100.00% | 100.00% | 0.00% |

much higher rate of GI symptoms (81.81%) compared to those who did not drink alcohol (64%). These findings suggest that smoking and alcohol consumption may further exacerbate the gastrointestinal side effects associated with Metformin use in patients with comorbidities (Table 3).

## Influence of antihypertensive medication on GI symptoms

Amlodipine was found to have the highest prevalence of gastrointestinal symptoms among patients with only Hypertension, with 59.09% of patients reporting symptoms. When Amlodipine was taken by patients with both Hypertension and Diabetes Mellitus, the prevalence of GI symptoms increased slightly to 65%. In contrast, Atenolol showed a lower incidence of GI symptoms in hypertension-only patients (25%), but the prevalence nearly doubled to 50% when Diabetes Mellitus was also present. Enalapril presented a middle-ground scenario, with a 33.33% prevalence of GI symptoms in hypertension-only patients (Table 4).

## Discussion

A study examining Metformin-induced gastrointestinal symptoms in patients with comorbidities such as Diabetes Mellitus, Hypertension, and coronary artery disease (CAD) revealed a notable prevalence rate of


https://doi.org/10.46389/rjd-2025-1840

Table 3: Distribution of GI symptoms among patients with various conditions, stratified by smoking and alcohol consumption status.

| S.No | Disease condition | Smoker | | Non-smoker | | Alcoholic | | Non-alcoholic | |
|---|---|---|---|---|---|---|---|---|---|
| | | GI symptoms | | | | | | | |
| | | Present | Absent | Present | Absent | Present | Absent | Present | Absent |
| 1. | Patients with Diabetes Mellitus taking Metformin (N=72) | 19 (54.28%) | 16 (45.72%) | 20 (54.05%) | 17 (45.95%) | 18 (54.54%) | 15 (45.45%) | 21 (53.85%) | 18 (46.15%) |
| 2. | Patients with Diabetes Mellitus and hypertension taking metformin (N=36) | 11 (91.6%) | 1 (8.3%) | 14 (58.33%) | 10 (41.66%) | 9 (81.82%) | 2 (18.18%) | 16 (64%) | 9 (36%) |
| 3. | Patients with hypertension (N=25) | 6 (66.66%) | 4 (44.44%) | 9 (56.25%) | 7 (43.75%) | 5 (71.42%) | 2 (28.58%) | 10 (55.56%) | 8 (44.44%) |
| 4. | Patients with coronary artery disease, hypertension and Diabetes Mellitus taking Metformin (N=34) | 9 (90%) | 1 (10%) | 17 (70.84%) | 7 (29.16%) | 9 (90%) | 1 (10%) | 17 (70.83%) | 7 (29.16%) |
| 5. | Patients with coronary artery disease (N=33) | 12 (66.67%) | 6 (33.33%) | 11 (73.33%) | 4 (26.67%) | 10 (62.5%) | 6 (37.5%) | 14 (82.35%) | 3 (17.64%) |

75.75% among CAD patients. It's noteworthy that these findings align with existing literature which suggests that 20–30% of individuals on Metformin experience gastrointestinal side effects [14, 15]. The data from the table indicates that this percentage can be even higher, especially in patients with multiple conditions like CAD and Hypertension.

The data shows that elderly patients with both Diabetes Mellitus and Hypertension, taking Metformin, exhibited significantly higher gastrointestinal symptoms (69.44%) compared to those with only Diabetes Mellitus (54.16%) or Hypertension (56%). The findings highlight the intensified impact of comorbid conditions on Metformin-induced GI symptoms. In a prior study, factors like older age, female gender, and the G allele were linked to metformin intolerance. Transporter-inhibiting drugs further amplified intolerance risk, emphasizing the need for personalized Metformin therapy considering these factors [14].

Patients with both Diabetes Mellitus and Hypertension, taking Metformin, exhibit a relative risk of 1.28, indicating a 28% higher likelihood of gastrointestinal symptoms compared to those on Metformin alone. In the previous study, 3.2% of patients achieved ADA goals for BP, LDL cholesterol, and HbA1c among 1,372 diabetic hypertensive patients [15]. These results emphasize the challenges in managing complex comorbid conditions and Metformin-induced side effects.

Mostly, Abdominal pain is the common symptom across all groups, slightly higher in the Diabetes Mellitus and Hypertension group. This highlights the need to consider comorbid conditions like hypertension when managing GI symptoms in diabetic patients on Metformin as the risk of GI AEs such as abdominal pain,

Table 4: Comparison of gastrointestinal symptoms in patients treated with different antihypertensive drugs (Amlodipine, Atenolol, Enalapril, Furosemide).

| S.No | GI symptoms | Amlodipine (N=42) | Atenolol (N=8) | Enalapril (N=20) | Furosemide (N=16) |
|---|---|---|---|---|---|
| **1.** | Abdominal Pain | 15 | 3 | 5 | 5 |
| **2.** | Epigastric pain | 13 | 2 | 3 | 5 |
| **3.** | Heart burn | 20 | 1 | 5 | 5 |
| **4.** | Bloating | 9 | 0 | 2 | 2 |
| **5.** | Regurgitation | 4 | 1 | 2 | 1 |
| **6.** | Abdominal rumbling | 4 | 1 | 1 | 3 |
| **7.** | Empty feeling | 10 | 1 | 1 | 2 |
| **8.** | Nausea | 8 | 2 | 4 | 2 |
| **9.** | Vomiting | 5 | 1 | 1 | 3 |
| **10.** | Loss of Appetite | 4 | 2 | 3 | 1 |
| **11.** | Belching | 2 | 1 | 1 | 1 |
| **12.** | Hematemesis | 3 | 0 | 0 | 1 |
| **13.** | Flatulence | 2 | 0 | 0 | 1 |
| **14.** | Dysphagia | 2 | 0 | 0 | 1 |
| **15.** | Bloody stools | 4 | 0 | 0 | 1 |
| **16.** | Mucus stool | 0 | 0 | 0 | 0 |
| **17.** | Stools Frequent with pain | 6 | 1 | 1 | 2 |
| **18.** | Diarrhea | 3 | 2 | 3 | 1 |
| **19.** | Constipation | 1 | 1 | 1 | 0 |
| **20.** | Frequent with Hard | 1 | 0 | 0 | 0 |

nausea and diarrhea is higher in T2DM patients treated with Metformin compared to other antidiabetic drugs or placebo [16, 17]. Abdominal pain was the most frequently reported symptom among all antihypertensive drugs analyzed, particularly in patients using Amlodipine. Bloating was also more common with Amlodipine but less frequent among Atenolol and Enalapril users. Additionally, nausea and vomiting were notable symptoms across the different medications. The literature showed that anti-hypertensive medications like verapamil (calcium channel blocker) can lead to constipation, while β blockers and ACE inhibitors may cause diarrhea due to their pharmacological effects [18–20].

The data suggests a strong correlation between smoking and gastrointestinal (GI) symptoms among patients with both diabetes and hypertension using Metformin. Smokers consistently report higher rates of GI issues across different patient subgroups, underscoring the need for targeted interventions addressing smoking cessation and GI symptom management, especially in high-risk populations. The results are supported by the studies that cigarette smoke adversely affects gastrointestinal health by damaging mucosal cells, impeding regeneration, reducing mucosal blood flow, and disrupting the immune system, which contributes to functional GI symptoms like abdominal pain, bloating, and constipation [17]. The data reveals a notable association between alcohol consumption and increased gastrointestinal (GI) symptoms in patients with both diabetes and hypertension, particularly among those taking Metformin. This suggests a potential exacerbating effect of alcohol on GI issues in individuals with these coexisting conditions, warranting attention to clinical management and lifestyle interventions.

These results resonate with existing studies suggesting that chronic ethanol (found in alcoholic beverages) can impact the integrity of the small intestinal


https://doi.org/10.46389/rjd-2025-1840

villi. Additionally, a single oral dose of ethanol has been shown to increase gastroduodenal permeability. Both these factors could potentially contribute to the exacerbation of GI symptoms, especially in patients already predisposed due to conditions like Diabetes Mellitus and Hypertension or medications like Metformin. The data underscores the intricate relationship between alcohol consumption, underlying conditions, and medication in influencing gastrointestinal symptom prevalence, emphasizing the need for holistic patient management [18].

Patients diagnosed with coronary artery disease and Hypertension along with Diabetes tend to experience higher rates of specific symptoms, notably abdominal pain and heartburn. This indicates that the presence of multiple conditions exacerbates the severity of Metformin-induced gastrointestinal issues. The data implies a correlation between comorbidities (such as Coronary Artery Disease and Hypertension) and the prevalence of Metformin-induced gastrointestinal symptoms. Elderly patients with diabetes and additional comorbidities face an elevated risk of experiencing these side effects, especially abdominal pain and heartburn, possibly due to the complex interplay of multiple health conditions and medication interactions [19].

Medications like Atorvastatin and Enalapril show a relatively higher prevalence of GI symptoms across various categories, with percentages ranging from 76.47% to 100%. The data highlights notable variability in the occurrence of GI symptoms across different antihypertensive medications. For instance, Atorvastatin and Enalapril consistently exhibit higher percentages of GI symptoms, emphasizing the need for vigilant monitoring when prescribing these drugs [20].

## Conclusions

This study makes a very high impact of comorbid conditions on the symptoms of Metformin-induced GI in elderly T2DM. The study presents a significant relation between the concomitant disorders, such as HTN and CAD, that have increased incidents of GI symptomatology. Patients with diabetes and hypertension showed a significantly higher prevalence of GI symptoms (69.44%) compared to patients with diabetes alone (54.16%) or hypertension alone (56%). The highest prevalence was found in patients with diabetes, hypertension, and CAD, where 70.83% of the patients complained of GI discomfort. The specific symptoms included abdominal pain, reported by 56.4% with diabetes only, 73% with CAD, diabetes, and hypertension and 64% of the group with diabetes and hypertension. Other common symptoms were heartburn, which was reported by 56.4%, 64%, and 60.75% of the above groups, respectively. Nausea and vomiting also occurred commonly, particularly in patients with multiple comorbidities, such as vomiting in 50% of patients with CAD, diabetes, and hypertension.

Furthermore, lifestyle conditions such as smoking and alcohol intake also contributed significantly to GI symptoms. Among those suffering from diabetes and hypertension and under Metformin, the smokers had a 91.6% prevalence of GI symptoms as opposed to 58.33% of the non-smokers. Likewise, alcoholism also contributed to a synergistic effect with a high GI symptom rate of 81.81% compared to 64% in the non-alcoholics, further demonstrating the adverse impact of lifestyle conditions and comorbidities in aggravating Metformin adverse effects. The choice of antihypertensive medication also influenced symptom severity. Amlodipine users had the highest rate of abdominal pain (15 cases), followed by Enalapril users (5 cases), while Atenolol users reported the least (3 cases). Notably, bloating and heartburn were significantly higher in patients on Amlodipine, while nausea and vomiting were most frequent among Enalapril users. These results highlight the need for personalized pharmacotherapy to counteract the additive insults exerted by Metformin and antihypertensive medication on GI health. Elderly diabetic patients with comorbid conditions deserve more individualized pharmacological management to avoid adverse effects, and personalized therapy might include dose reduction, alternative treatments, and lifestyle modification, which may be crucial to improve diabetes management in these patients while minimizing the impact of GI side effects. Pharmacogenetic influences, as well as alternative treatment regimens, may be investigated further to better enhance Metformin tolerability among high-risk elderly subjects.

## Acknowledgments

We are grateful to the staff of JKKN College of Pharmacy for their unwavering support throughout the research process. Special thanks to the experts in endocrinology, geriatrics, and pharmacology who helped validate the questionnaire and provided constructive feedback.

## Conflict of interest

The authors declare no conflict of interest.

## Ethics approval

This study followed the ethical considerations defined by the Institutional Ethics Committee of J.K.K. Nattraja College of Pharmacy. The research proposal, "A Prospective Study on the Relationship between Comorbidities and Metformin-Induced Gastrointestinal Symptoms in Elderly Patients with Diabetes", was reviewed and approved by the IEC (Approval Number: JKKNCP/IEC-CER/0422123/38) on May 22, 2023. Informed consent was taken from all participants through a written format, ensuring their voluntary participation, confidentiality, and the right to withdraw at any stage without any repercussions. The study ensured adherence to all institutional and national ethical guidelines for human research.

## Consent to participate

Written informed consent was obtained from all the participants.

## References


1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32 Suppl 1(Suppl 1): S62-S67. doi:10.2337/dc09-S062
2. Standl E, Khunti K, Hansen TB, Schnell O. The global epidemics of diabetes in the 21st century: Current situation and perspectives. European Journal of Preventive Cardiology. 2019;26(2_suppl):7-14. doi:https://doi.org/10.1177/2047487319881021
3. Druss BG, Marcus SC, Olfson M, Tanielian T, Elinson L, Pincus HA. Comparing the national economic burden of five chronic conditions. Health Aff (Millwood). 2001;20:233-41. 10.1377/hlthaff.20.6.233
4. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: the health and retirement study. J Am Geriatr So.c 2009;57:511-6. 10.1111/j.1532-5415.2008.02150.x
5. Schneider KM, O'Donnell BE, Dean D. Prevalence of multiple chronic conditions in the United States' Medicare population. Health Qual Life Outcomes. 2009;7:82. 10.1186/1477-7525-7-82
6. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med. 2002;162:2269-76. 10.1001/archinte.162.20.2269
7. Schlender L, Martinez YV, Adeniji C, et al. Efficacy and safety of metformin in the management of type 2 diabetes mellitus in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. BMC Geriatrics. 2017;17(S1). doi:https://doi.org/10.1186/s12877-017-0574-5
8. Nabrdalik K, Skonieczna-Żydecka K, Irlik K, et al. Gastrointestinal adverse events of metformin treatment in patients with type 2 diabetes mellitus: A systematic review, meta-analysis and meta-regression of randomized controlled trials. Front Endocrinol (Lausanne). 2022;13:975912. Published 2022 Sep 14. doi:10.3389/fendo.2022.975912
9. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17(6):571-584. doi:10.2174/092986710790416326
10. Jang K, Chung H, Yoon J, et al. Pharmacokinetics, Safety, and Tolerability of Metformin in Healthy Elderly Subjects. The Journal of Clinical Pharmacology. 2016;56(9):1104-1110. doi:https://doi.org/10.1002/jcph.699
11. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016;65(2):20-29. doi:https://doi.org/10.1016/j.metabol.2015.10.014
12. Florez H, Luo J, Castillo-Florez S, et al. Impact of metformin-induced gastrointestinal symptoms on quality of life and adherence in patients with type 2 diabetes. Postgrad Med. 2010;122(2):112-120. doi:10.3810/pgm.2010.03.2128
13. Kawamura T, Umemura T, Hotta N. Cognitive impairment in diabetic patients: Can diabetic control prevent cognitive decline?. J Diabetes Investig. 2012;3(5):413-423. doi:10.1111/j.2040-1124.2012.00234.x
14. Dujic T, Causevic A, Bego T, et al. Organic cation transporter 1 variants and gastrointestinal side effects of metformin in patients with Type 2 diabetes. Diabetic Medicine. 2016 Apr;33(4):511-4.
15. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Annals of Internal Medicine. 2002;137(1):25-33.
16. Nabrdalik K, Skonieczna-Żydecka K, Irlik K, et al. Gastrointestinal adverse events of metformin treatment in patients with type 2 diabetes mellitus: A systematic review, meta-analysis and meta-regression of randomized controlled trials. Front Endocrinol (Lausanne). 2022;13:975912.
17. Keshavarzian, A., Fields, J., Vaeth, J., & Holmes, E. (1994). The differing effects of acute and chronic alcohol on gastric and intestinal permeability. The American journal of gastroenterology.1994;89 (12): 2205-11 .
18. Bassotti G, Calcara C, Annese V, et al. Nifedipine and verapamil inhibit the sigmoid colon myoelectric response to eating in healthy volunteers. Diseases of the Colon & Rectum. 1998;41:377–80.
19. LI LF, CHAN RLY, LU L, et al. Cigarette smoking and gastrointestinal diseases: The causal relationship and underlying molecular mechanisms (Review). International Journal of Molecular Medicine. 2014;34(2):372-380.
20. Abrahamsson H, Lyrenas E, Dotevall G. Effects of beta-adrenoceptor blocking drugs on human sigmoid colonic motility. Digestive Diseases and Sciences.1983;28:590–4.


 https://doi.org/10.46389/rjd-2025-1840 