Frequency of Gastroesophageal Reflux in Diabetic Patients without Gastrointestinal Symptoms

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ABSTRACT

Objective: Diabetes Mellitus (DM) represents a complex metabolic disorder characterized by chronic hyperglycemia resulting from insulin dysfunction. Numerous studies have underscored the prevalence of gastrointestinal complications in individuals with DM, gastrointestinal complications in DM patients primarily stem from changes in gastrointestinal motility patterns. This study aimed to investigate the prevalence of asymptomatic Gastroesophageal Reflux Disease (GERD) in patients with DM due to the frequent occurrence of gastrointestinal (GI) complications in DM patients, which are often underdiagnosed owing to their asymptomatic nature. We further aimed to elucidate the potential correlations between GERD and peripheral neuropathy in DM patients.

Materials and Methods: Within this prospective study, 20 patients diagnosed with DM and without symptoms of GERD were selected from the Internal Medicine and Gastroenterology outpatient clinics. Patients were diagnosed with the primary method of GERD detection 24-hour ambulatory pH monitoring. Patients, devoid of any GERD symptoms and dyspepsia, were assessed through a dyspepsia questionnaire, followed by determining fasting glucose levels, HbA1c values, and Body Mass Index (BMI) calculations. Subsequent evaluations involved esophageal manometry and 24-hour ambulatory.

Results: The evaluation of results using 24-hour ambulatory pH meter testing revealed a 40% prevalence of GERD in asymptomatic DM patients (8 out of 20 patients). A comparative analysis between DM patients with and without GERD, based on age, sex, BMI, HbA1c values, and fasting blood glucose levels, demonstrated no statistically significant differences. However, the frequency of GERD was significantly elevated in asymptomatic DM patients compared to the general population in our country (p<0.05).

Conclusion: The findings indicate that 40% of DM patients exhibit GERD even in the absence of symptoms, highlighting the ubiquity of GI symptoms and complications in DM patients. This underscores the critical need for enhanced vigilance and proactive measures for GERD complications in this demographic. Implementing precise dietary plans, lifestyle modifications, and appropriate pharmacologic interventions can substantially ameliorate the quality of life and thwart GERD-related complications, even in DM patients not manifesting overt GERD symptoms.

Keywords: Diabetes Mellitus, Gastroesophageal Reflux Disease, Asymptomatic GERD, Peripheral Neuropathy, Esophageal Manometry, 24-hour Ambulatory pH Meter Testing.

INTRODUCTION

Diabetes Mellitus (DM) epitomizes a multifaceted metabolic disorder characterized by chronic hyperglycemia due to insulin dysfunction. A plethora of studies have highlighted the prevalence of gastrointestinal complications among individuals diagnosed with DM (1). Primarily, manifestations of gastrointestinal complications in DM patients are attributed to alterations in motility patterns within the gastrointestinal tract.
The precise incidence of GI symptoms associated with DM remains elusive; the existing literature illustrates a divergence in empirical evidence. Some studies purport that the likelihood of developing DM-related complications is 3 to 4 times higher in individuals with diabetes, transcending gender disparities (2). In contrast, alternate scholarly articles posit no substantial variance between the diabetic population and the general populace regarding gastrointestinal complications (3).

Gastrointestinal disorders prevalent in DM patients are often categorized under neuropathy—a prevalent complication in DM—owing to the pathological alteration of nerves (4,5,6,7,8). Despite the prevalence, the etiological foundations of GI motility disorders remain a topic of scientific conjecture. However, a consensus is emerging around the hypothesis that the motor dysfunction is an intricate consequence of neurological complications inherent in DM (9,10). Bytzer’s seminal work ascertains these disorders as ramifications of peripheral neuropathy in the context of DM (7,8,11).

Gastroesophageal reflux (GER) is defined as a multifaceted and persistent gastrointestinal disorder, emerging as one of the predominant diseases affecting the GI tract. Given the potential complications of chronic GER, including chronic sinus infections, dental anomalies, Barrett’s esophagus, and esophageal adenocarcinoma, early diagnosis and intervention are imperative.

The concurrent prevalence of DM and GERD posits a plausible intersection of clinical conditions, yet the empirical narratives on the incidence of GERD within the DM demographic are characterized by a plethora of contradictory findings (12,13).

Ambulatory 24-hour pH monitoring has been canonized as the gold standard for diagnosing pathological reflux, boasting a sensitivity range of 77–100% and specificity of 85–100% for patients exhibiting endoscopic esophagitis (14). This modality operates through the attachment of a nasal catheter or capulse to the distal esophageal mucosa, enabling patients to maintain their usual diet. Subsequently, the resultant data are interpreted utilizing specialized computer programs to calculate the Standard De Meester score, considering various acid reflux-related parameters (15,16,17,18). A score exceeding 14.7 is indicative of abnormal acid reflux (15, 19).

While the relationship between DM and gastrointestinal complications has been established, the prevalence of GERD in asymptomatic DM patients remains underexplored (13-15). The existing literature provides fragmented insights, often overlooking the silent manifestations of GERD that may occur without typical esophageal symptoms. This gap is critical as it impedes the full understanding of GERD’s impact on the diabetic population and the potential need for preemptive clinical interventions. Our study aims to bridge this knowledge gap by evaluating the frequency of asymptomatic GERD in patients with DM through non-invasive diagnostic methods. By doing so, we seek to illuminate the hidden burden of GERD in this population and underscore the importance of considering GERD in the differential diagnosis of DM patients, regardless of the presence of traditional symptoms.

This study endeavors to discern the existence and quantify the frequency of gastroesophageal reflux disease in a cohort of DM patients devoid of esophageal symptoms, leveraging the non-invasive 24-hour ambulatory pH monitoring technique. The study incorporated a diverse sample of outpatient DM individuals presenting no dyspeptic complaints or manifested reflux symptoms.

**MATERIAL and METHODS**

This research was conducted as a prospective study involving 20 patients diagnosed with DM — comprising eight women and twelve men. Our Internal Medicine and Gastroenterology outpatient clinics comprehensively examined the patients for various concerns.

**Participants**

The cohort for this study consisted of individuals with a prior diagnosis of DM, showing no symptoms or diagnostic history of reflux or dyspepsia, and not using proton pump inhibitors (PPIs) and H2 receptor antagonists (H2Rs) for any underlying conditions. The selection criterion also necessitated the absence of dyspepsia as per the ROME III dyspepsia questionnaire and no prior upper gastrointestinal endoscopy. Comprehensive data, including age, gender, duration of diabetes, medications, and complications, were meticulously documented.

**Study Design**

The primary step involved the meticulous investigation of any symptoms pertinent to GERD (including retrosternal burning, regurgitation, water-brash) within the patient cohort. Those exhibiting no symptoms were further analyzed using the ROME III criteria.

Subsequently, every participant underwent a detailed evaluation through the Rome III dyspepsia module (20), esophageal manometry, and ambulatory 24-hour esophageal pH monitoring if they displayed no indicators of dyspepsia. Parameters such as height, weight, body mass index, fasting blood glucose levels, and hemoglobin A1c (HbA1c) levels were meticulously recorded at the study’s inception. Antidiabetic treatment protocols were also evaluated and recorded meticulously. Post esophageal pH monitoring, and comparative analysis were conducted between patient groups exhibiting reflux and those without, considering variables like body mass index, fasting blood glucose level, and HbA1c levels.

The interpretation of pH monitoring results included comprehensive analyses of De Meester scores, total reflux time, the number of reflux periods, instances of reflux periods extending beyond 5 minutes, and the maximum duration of reflux.

In this study, esophageal manometry was performed using a high-resolution manometer, with patients in a supine position to measure the esophageal motility and lower esophageal sphincter (LES) function.
The manometry probe was positioned to record pressures from the hypopharynx to the stomach, capturing LES relaxation and contraction patterns. For 24-hour ambulatory pH monitoring, a dual-sensor pH catheter was placed transnasally and positioned with one sensor at 5 cm above the LES and the other at 15 cm.

The criteria for abnormal pH monitoring results were defined as an acid exposure time (percent time pH < 4) greater than 4.2% over 24 hours, or a DeMeester score greater than 14.7, which are indicative of pathological acid reflux. The pH data were continuously recorded as patients maintained their usual activities and diet, ensuring the monitoring reflected their typical daily acid exposure.

**Statistical Analysis**

This study was powered to detect a medium effect size (Cohen’s d) of 0.5 with 80% power at a 5% significance level, ensuring that the findings regarding the prevalence of GERD in asymptomatic diabetic patients are robust and statistically reliable. The statistical analysis was conducted utilizing the NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). A myriad of statistical tests, including Student’s t-test, Mann Whitney U test, Chi-square test, and Fisher's Exact test were deployed for comparative analysis and evaluation of study data, alongside descriptive statistical methods (mean, standard deviation, median, frequency, ratio). A significance level of p<0.05 was maintained for assessing each parameter.

**Results**

This research endeavor focused on twenty patients diagnosed with DM, who exhibited neither dyspeptic complaints nor symptoms of reflux. An analytical assessment between patients manifesting reflux and those without, based on age and gender, unveiled no substantial distinction between diabetic patients in both categories (p>0.05).

The mean Body Mass Index (mean ± SD) was 32.62 ± 9.68 kg/m² for patients exhibiting reflux and 29.44 ± 4.25 kg/m² for those without reflux. The comparative analysis regarding mean Body Mass Index values revealed no statistically significant discrepancies between the cohorts of diabetic patients with and without reflux (P=0.20).

Upon scrutinizing the mean fasting blood glucose values (mean ± SD) at the time of the study inception, the results manifested no discernible statistical differences between the cohorts with and without reflux (P=0.11). The derived mean fasting blood glucose values were 142.1 ± 24.5 mg/dL in the cohort with reflux and 162.5 ± 47.5 mg/dL in the cohort devoid of reflux.

The current mean HbA1c levels (mean ± SD) at the initiation of the study were 8.06% ± 1.49% in patients without reflux and 6.93 ± 0.66% in patients with reflux. A meticulous evaluation concerning hemoglobin A1c levels presented no statistically significant variances between diabetic patients with and without reflux (P=0.25).

A comprehensive depiction of the patients’ clinical and demographic characteristics is elaborated in Table 1 and Table-2 respectively.

**Table 1: The clinical characteristics of the patients**

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Gender</th>
<th>DM (year)</th>
<th>DM Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>30</td>
<td>Insulin</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>6</td>
<td>Insulin + OAD**</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>M</td>
<td>&lt;1</td>
<td>OAD</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>F</td>
<td>&lt;1</td>
<td>OAD</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>M</td>
<td>5</td>
<td>OAD</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>F</td>
<td>8</td>
<td>Insulin+ OAD</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>F</td>
<td>&lt;1</td>
<td>Insulin</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>M</td>
<td>6</td>
<td>Insulin</td>
</tr>
<tr>
<td>9</td>
<td>79</td>
<td>M</td>
<td>9</td>
<td>Insulin+OAD</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>F</td>
<td>6</td>
<td>OAD</td>
</tr>
<tr>
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<td>M</td>
<td>11</td>
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<td>13</td>
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<td>M</td>
<td>17</td>
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<td>16</td>
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<td>2</td>
<td>OAD</td>
</tr>
<tr>
<td>17</td>
<td>61</td>
<td>F</td>
<td>10</td>
<td>OAD+ Insulin</td>
</tr>
<tr>
<td>18</td>
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<td>OAD</td>
</tr>
<tr>
<td>19</td>
<td>81</td>
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<td>20</td>
<td>OAD</td>
</tr>
<tr>
<td>20</td>
<td>41</td>
<td>F</td>
<td>5</td>
<td>OAD</td>
</tr>
</tbody>
</table>

* Insulin: short acting, mixed and long acting insulin.
**OAD: Oral Antidiabetic Drugs.
M: male F: female

**Table 2: Demographic characteristics of the patients**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>8 (%40)</td>
<td>12 (%60)</td>
</tr>
<tr>
<td>Age</td>
<td>37–81</td>
<td>37–81</td>
<td>37–79</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>55.4 ± 13.9</td>
<td>54.1 ± 13.4</td>
<td>56.2 ± 14.9</td>
</tr>
</tbody>
</table>

* Student’s t-test, P=0.749

*P > 0.05
DISCUSSION

Our study, employing a non-invasive, objective method—pH monitoring—established that the prevalence of gastroesophageal reflux in patients with DM was 40%. This finding is notably higher (20%) than the outcomes documented in a study exploring the general population in our country (21). It aligns with other global studies, where the reported prevalence of GERD in the general populace is recorded as substantially lower, at 14% (22). Wong et al. highlighted in their study a significantly heightened prevalence of gastroesophageal reflux in DM patients with diabetic neuropathy compared to the general populace (43.5% versus 14%) (22).

The frequency of GERD discerned in this study coheres with the data scrutinized in our research. Nonetheless, the study of Wong et al. principally probed the manifestation of reflux symptoms, whereas our analysis was predicated on authenticating the presence of objective reflux using pH meters in asymptomatic patients (22).

Historical data illustrate that the occurrence of esophageal symptoms in diabetic patients oscillates between 2% and 27% (23), however, pyrosis was not evaluated as a symptom allied with DM in these studies. As our focus was on asymptomatic patients, none exhibited pyrosis. In utilizing the 24-hour ambulatory pH monitoring method, which is acknowledged as the most accurate technique to detect reflux, it was discovered that a significant 40% of our patient sample experienced notable reflux, a finding that is congruent with similar studies.

Our outcomes resonate with the findings of Murray et al., wherein, utilizing a comparable method, the prevalence of reflux in asymptomatic diabetic patients was 45% (13). Nishida et al. documented a 20% prevalence of reflux using 24-hour ambulatory pH monitoring (26). Interestingly, this study delineated that while the prevalence of reflux was higher in DM patients overall, this prevalence escalated in those with cardiovascular diabetic neuropathy.

Moreover, a study from Korea found that the prevalence of reflux was particularly high (23.1%) in Type 2 DM patients who reported experiencing typical reflux symptoms at least once a week (27). Our study, however, did not explore the manifestations of diabetes-related autonomic neuropathy; thus, we did not categorize our patients based on autonomic neuropathy, focusing instead on assessing the frequency of reflux in asymptomatic diabetic patients compared to the general population.

The etiological underpinnings of elevated gastrointestinal symptoms in patients with Type 2 DM, and the mechanisms prompting this increased frequency, remain to be elucidated. Several speculative variables, including overweight and obesity, the array of drugs used for DM treatment, the duration of DM, blood glucose values at diagnosis, and DM complications, are all in consideration. Overweight and obesity are acknowledged risk factors for GERD, with several studies elucidating a correlation between BMI and GERD symptoms, even in patients with average body weight (25, 28, 29, 30).

In this research endeavor, the majority of the participants were either overweight or obese based on their BMI values. However, a comparative analysis between DM patients with and without reflux based on BMI revealed no significant disparities (p=0.18), negating the proposition that BMI is a contributing factor to the incidence of gastroesophageal reflux disease in DM patients.

Furthermore, our study endeavored to draw correlations between blood glucose values and HbA1c values, finding no significant disparities between DM patients with and without reflux (p=0.12 and p=0.31, respectively), which suggests that glycemia and HbA1c values are not indicative of GERD risk in DM patients.

The literature presents a myriad of studies with divergent results on this matter. Bytzer et al. (4) posited that gastrointestinal symptoms in DM patients correlated with DM complications but failed to establish a significant correlation between blood glucose and HbA1c levels and symptoms. However, another study from the same group drew a correlation between gastrointestinal symptoms, poor glycemic control, and DM complications (11).

It should be acknowledged that gastrointestinal complications and symptoms are not uncommon in DM patients, particularly in Type 2 DM patients, who exhibit higher instances of GERD symptoms compared to the general populace. Based on the objective methodologies implemented, our study ascertains that GERD is indeed more prevalent in DM patients compared to the general population. Therefore, it’s imperative that a thorough evaluation for GERD is conducted in DM patients, regardless of the presence of gastrointestinal symptoms, through meticulous history taking, comprehensive physical examinations, appropriate laboratory tests, and if necessary, upper gastrointestinal endoscopy and pH meter examination. Early interventions, lifestyle modifications, and appropriate pharmacological treatments can significantly enhance the quality of life and mitigate GERD-related complications in DM patients, even in the absence of overt GERD symptoms.

In our investigation of GERD prevalence among diabetic patients, we also sought to explore the potential correlation with peripheral neuropathy, considering its prevalence in diabetic complications. While our data did not reveal a statistically significant correlation between GERD and peripheral neuropathy within our sample, this finding itself is informative. It suggests that the mechanisms contributing to GERD in diabetes may be multifactorial and not solely dependent on neuropathic changes. Factors such as glycemic control, the duration of diabetes, and autonomic function might also play roles in developing GERD, independent of peripheral neuropathy. Future studies may focus on these variables to elucidate their contributions to GERD in the diabetic population.

Study Limitations

This study’s insights, while informative, are circumscribed by several limitations. The sample size is relatively constrained, potentially limiting the external validity and generalizability of the findings to the broader population of patients with DM. The lack of exploration of diabetes-related autonomic neuropathy in our participants prevents a more nuanced understanding of the interaction between neuropathy and the prevalence of gastroesophageal reflux, leaving room for
subsequent research to explore these interrelationships more deeply.

The concentration solely on asymptomatic diabetic patients could be constraining the thoroughness of insights, potentially overlooking symptomatic patients’ experiences and correlations with GERD. Furthermore, the study did not consider the variations in the lifestyle, dietary habits, and the level of physical activity among the participants, which could significantly impact the prevalence of GERD.

This study also did not factor in different types and stages of diabetes or control for concurrent medications, which could have provided more nuanced insights into the correlations between different diabetic conditions, treatment regimens, and GERD.

CONCLUSION

This study’s findings underscore the heightened prevalence of GERD in patients with DM, notably in those who are asymptomatic, compared to the general population. It brings to the fore the imperative need for comprehensive and proactive medical evaluations for GERD in all DM patients, irrespective of the manifestation of overt gastrointestinal symptoms, due to the potential risks and complications associated with untreated GERD. The early detection and management of GERD, via meticulous clinical evaluations, diet, lifestyle alterations, and optimal pharmacological interventions, can significantly ameliorate the quality of life and curtail GERD-related complications in individuals with Diabetes Mellitus.

The apparent correlation between DM and GERD prevalence emphasizes the necessity for further extensive, nuanced, and diversified research. Future studies with larger, more diverse sample sizes and inclusive of various diabetic conditions and symptoms are essential to deepen the understanding of the intricate relationships between Diabetes Mellitus and gastroesophageal reflux disease, and to refine the diagnostic and therapeutic strategies for optimal patient outcomes.

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Author Contributions: NMD, OUB, AMÖ: Designed and directed the study, Literature search, Data collection, Statistics NMB, OUB, AMÖ, AB: Article writing, Final revisions. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee. Ethics Committee approval: The protocol for this study received approval from the Clinical Research Ethics Committee of Istanbul Maltepe University (Protocol date and number: 16.09.2009/ 5)

REFERENCES


