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Association between sitagliptin use and recurrent urinary tract infection in patients with type 2 diabetes mellitus; a case–control study

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ABSTRACT

Introduction: Recurrent urinary tract infections (UTIs) are a frequent and clinically important complication in patients with type 2 diabetes mellitus (T2DM), contributing to substantial morbidity and healthcare utilization. The risk of UTI in this population may be influenced not only by chronic hyperglycemia and diabetes-related comorbidities, but also by specific glucose-lowering therapies. Sitagliptin, a widely used dipeptidyl peptidase-4 (DPP-4) inhibitor, is generally considered to have a favorable safety profile; however, data on its potential association with recurrent UTI remain limited and somewhat inconclusive.

Objectives: This study aimed to evaluate whether sitagliptin use is associated with recurrent UTI in adults with type 2 diabetes.

Materials and Methods: This case–control study included adults with T2DM referred to Labbafinezhad Hospital, Tehran, Iran (October 2025–May 2026), who were classified as cases (recurrent UTI) or controls (no recurrent UTI) according to standard recurrence criteria. Eligible patients had been treated during the preceding year with either metformin alone or metformin plus sitagliptin; those exposed to other oral or injectable anti-diabetic agents were excluded. Data on demographics, comorbidities, urological history, diabetes duration, anti-diabetic therapy, and HbA1c were collected through structured interviews and review of medical records after written informed consent. Sitagliptin use (user vs non-user) was defined based on the preceding year's regimen, and its association with recurrent UTI (yes/no) was evaluated using binary logistic regression.

Results: The binary logistic regression indicated that sitagliptin use was not significantly associated with recurrent UTI, both in the unadjusted model (odds ratio [OR] 1.09, 95% confidence interval [CI] 0.58–2.04, $P=0.773$) and after adjustment for demographic and clinical confounders (OR 1.13, 95% CI 0.57–2.23, $P=0.721$).

Conclusion: Sitagliptin use was not associated with an increased risk of recurrent UTI among patients with T2DM, suggesting that this agent appears safe with respect to UTI recurrence in this population.

Implication for health policy/practice/research/medical education:
In this study of adults with type 2 diabetes mellitus (T2DM), the results indicated that sitagliptin use was not significantly associated with the odds of recurrent urinary tract infection (UTI), and this null association persisted after adjustment for key demographic and clinical confounders. Overall, these findings suggest that sitagliptin therapy does not independently increase the risk of recurrent UTI among patients with T2DM, and that other patient- or disease-related determinants are more likely to underlie UTI recurrence in this population.

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Original

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic disorders globally, defined by progressive insulin resistance and deteriorating beta-cell function, and it continues to impose an enormous burden on healthcare systems worldwide (1,2). According to the International Diabetes Federation (IDF), the number of adults living with diabetes reached approximately 537 million in the age range of 20 to 79 years, representing 10.5% of the world's adult population, with projections estimating that this figure will rise to 783 million by 2045 (3,4). Among the most clinically significant yet frequently underappreciated complications of T2DM are infectious diseases, particularly urinary tract infections (UTIs), which occur at substantially higher rates in diabetic individuals than in the general population (5-8). The previous studies demonstrated that patients with T2DM had a higher risk of developing UTIs compared with non-diabetic controls, with female sex, advancing age, and a prior history of UTI emerging as the most consistent independent risk factors (8-10). Importantly, diabetic patients do not merely contract UTIs more often; they also experience more severe clinical trajectories, with higher rates of bacteremia, greater frequency of hospitalizations, and substantially elevated mortality compared with non-diabetic counterparts (11).

Recurrent UTI, conventionally defined as two or more documented symptomatic episodes within six months or three or more within twelve months, represents a particularly challenging clinical entity in patients with T2DM (12-14). A systematic review encompassing fifteen studies from ten countries confirmed that four out of five studies examining this relationship found diabetes to be a statistically significant independent risk factor for recurrent UTI, with recurrence rates ranging from 23.4% to 37% across different diabetic cohorts (7). Studies corroborated these findings, reporting that women with diabetes had meaningfully higher UTI recurrence rates than their non-diabetic counterparts (15). These findings collectively underscore the clinical urgency of identifying modifiable risk factors for recurrent UTI within the T2DM population, including factors arising from glucose-lowering pharmacotherapy itself.

Sitagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, has become one of the most widely prescribed oral anti-hyperglycemic agents for T2DM owing to its favorable glucose-lowering efficacy, low risk of hypoglycemia, weight-neutral profile, and good tolerability across a broad range of patient subgroups (16,17). The mechanism of action involves inhibition of the DPP-4 enzyme, thereby prolonging the activity of endogenous incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), to augment glucose-dependent insulin secretion and suppress inappropriate glucagon release (17,18). Of relevance to infectious outcomes, DPP-4 is not exclusively a metabolic enzyme; it is also expressed on the surface of immune cells, including T lymphocytes, where it participates in the regulation of cytokine and chemokine signaling, raising theoretical concerns that sustained pharmacological inhibition could attenuate host immune defenses against pathogens, including uropathogens (19). A real-world cohort study using Korean national insurance data similarly found that DPP-4 inhibitors were not associated with increased risk of UTIs compared with metformin in insulin-treated T2DM patients. However, these aggregate analyses do not stratify by infection recurrence, do not specifically capture the subgroup of patients with pre-existing recurrent UTI susceptibility, and may lack the statistical resolution to detect a signal in high-risk subpopulations (20). Given the widespread and long-term use of sitagliptin in patients with T2DM, who are already predisposed to recurrent UTI through multiple disease-inherent mechanisms, the present case-control study aims to investigate whether sitagliptin use is independently associated with the occurrence of recurrent UTI in this population, a clinically relevant question that has yet to be addressed with dedicated pharmacoepidemiological methodology.

Objectives

This study aimed to investigate whether sitagliptin use is associated with the occurrence of recurrent UTI in adults with T2DM, before and after adjustment for major demographic and clinical confounders.

Materials and Methods

Study design and participants

This case–control study was conducted on patients with T2DM referred to Labbafinezhad hospital in Tehran, Iran, from October 2025 to May 2026. The study population comprised all eligible patients with and without recurrent UTI who met the predefined inclusion criteria. Participants were divided into two groups based on UTI recurrence status: cases included patients with recurrent UTI, while controls consisted of those without recurrent UTI. All participants were recruited from the same clinical setting to ensure comparability between groups.

Inclusion criteria and exclusion criteria

Eligible participants were adults with a confirmed diagnosis of T2DM who were receiving antidiabetic treatment and had available clinical and laboratory data. Patients were included if they had been treated consistently during the preceding year with either metformin monotherapy or a combination of metformin and sitagliptin, and if sufficient information was available to determine the presence or absence of recurrent UTI based on clinical history and medical records. Patients were excluded if they had a history of treatment with other oral or injectable anti-diabetic medications in the prior year to minimize potential drug-related confounding. Additional exclusion criteria included incomplete medical

records, inability to provide a reliable clinical history, or lack of consent to participate in the study.

Group classification

Participants were classified into two groups based on the presence or absence of recurrent UTI. The case group consisted of patients with T2DM who met the predefined criteria for recurrent UTI, while the control group included those without a history of recurrent UTI. In addition, participants were further categorized according to exposure status to sitagliptin. Patients who had received a combination of metformin and sitagliptin during the preceding year were classified as sitagliptin users, whereas those treated with metformin alone were considered non-users.

Recurrent UTI definition

For this study, recurrent UTI was defined as repeated symptomatic episodes of UTI meeting standard clinical criteria, operationalized as at least two acute UTI episodes within 6 months or three or more episodes within 12 months, in line with published guidelines and prior literature (12-14).

Data collection

Data were obtained using a combination of patient interviews and review of medical records, after obtaining written informed consent from all participants. During face-to-face interviews, trained research personnel collected socio-demographic information, clinical history, and details of current anti-diabetic therapy, including sitagliptin and metformin use, as well as any history of recurrent UTI. Relevant clinical data, such as documented comorbidities (e.g., hypertension [HTN], cardiovascular disease, benign prostatic hyperplasia [BPH]), prior urological surgery, diabetes duration, and laboratory parameters including HbA1c, were extracted from patients' interviews, medical charts, and electronic health records using a standardized data-abstraction form to ensure consistency and completeness across cases and controls. The method of examining sitagliptin use in the study subjects was as follows: patients classified as sitagliptin users were those who had been treated with a combination of metformin and sitagliptin during the previous year, whereas patients classified as non-users were those who had received metformin monotherapy during the same period, based on information documented in the medical records and confirmed by patient self-report. To minimize confounding by other anti-diabetic agents, all individuals with a history of treatment with additional oral or injectable diabetes medications in prior years were excluded from the study.

Outcomes measurement

The primary outcome of this case–control study was the association between sitagliptin exposure and the occurrence of recurrent UTI in individuals with T2DM. Recurrent UTI status (recurrent vs. non-recurrent) was defined a priori based on clinical criteria and documented through patient self-report corroborated by medical records and was operationalized as a binary dependent variable. Sitagliptin use was classified dichotomously (user vs. non-user) according to anti-diabetic treatment in the preceding year and served as the principal exposure variable. This exposure–outcome relationship was quantified using odds ratios (ORs) and 95% confidence intervals (CIs) derived from binary logistic regression models, with further adjustment for potential confounding factors in multivariable analyses.

Statistical analysis

Statistical analysis were performed using SPSS software, version 27 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test to evaluate normality. Quantitative variables with an approximately normal distribution were summarized as mean ± standard deviation and compared between patients with and without recurrent UTI using the independent samples t-test, whereas categorical variables were presented as frequencies and percentages and compared using the chi-square test. To examine the association between sitagliptin use and recurrent UTI, binary logistic regression models were constructed to estimate ORs and 95% CI, first in an unadjusted model and then in a multivariable model adjusting for age, sex, marital status, BMI, cardiovascular comorbidities, HTN, diabetes duration, HbA1c level, history of urological surgery, and BPH. A two-sided P value < 0.05 was considered statistically significant.

Results

The study population consisted of 161 individuals with T2DM, with a mean age of 51.55 years and a mean disease duration of approximately 7.5 years. The majority of participants were married women with a BMI in the slightly overweight range and without a history of underlying cardiovascular disease, prior urological surgery, or BPH. The statistical analysis indicated that baseline demographic and clinical characteristics were broadly comparable between those with and without recurrent UTI. Women and married individuals predominated in both groups, with no appreciable difference in gender or marital status distribution. The prevalence of HTN, cardiac disease, previous urological surgery, and BPH was also similar across groups. Likewise, mean age, BMI, and diabetes duration were similar between the two groups, and none of these variables differed significantly between the two groups, suggesting that the recurrent UTI and non-recurrent UTI cohorts were largely homogeneous with respect to measured baseline characteristics (Table 1).

The results also demonstrated that the clinical characteristics related to anti-diabetic treatment and

glycemic control were similar in those with and without recurrent UTI. The proportions of patients receiving metformin and sitagliptin did not differ meaningfully between the two groups, with both drugs being used by the majority of participants. Likewise, mean HbA1c levels were comparable, and no significant difference in overall glycemic control was observed between patients with recurrent UTI and those without (Table 2).

Binary logistic regression analysis showed no meaningful association between sitagliptin use and the occurrence of recurrent UTI. In the unadjusted model, the odds of recurrent UTI among sitagliptin users were similar to those among non-users, with an OR close to unity and not significant. After adjustment for multiple potential confounders, including age, sex, marital status, BMI, cardiovascular comorbidities, HTN, duration of diabetes, HbA1c level, history of urological surgery, and BPH, the OR remained close to one and was statistically non-significant. These findings indicate that sitagliptin consumption was not independently associated with an increased or decreased risk of recurrent UTI in this cohort of patients with T2DM (Table 3).

Discussion

The UTI represents one of the most prevalent and clinically consequential infectious complications in patients with T2DM. Compared with non-diabetic individuals, people living with T2DM experience both a higher incidence and a greater tendency toward recurrence. In a large matched cohort, Fu et al found that newly diagnosed T2DM subjects had UTI rates of 9.4% versus 5.7% in matched controls, with recurrent UTI rates of 1.6% versus 0.6%, corresponding to an adjusted OR of 1.54 (95% CI 1.47–1.60) (21). The epidemiological burden is further underscored by registry data from Germany, where UTI event rates in T2DM patients reached 87.3 per 1,000 patient-years, with prior UTI history emerging as among the strongest independent predictors (HR 2.77–5.94) (22). Against this background, a systematic review reported recurrence rates ranging from 23.4% to 37% in T2DM patients, with the majority of included studies identifying diabetes itself as an independent risk factor for recurrence (7). As the use of DPP-4 inhibitors such as sitagliptin has expanded substantially in the management of T2DM, questions have naturally arisen regarding whether this

Table 1. Frequency distribution of demographic profile among T2DM patients with and without recurrent UTI

Demographic data		Recurrent UTI		Total	*P* value*
		No (n = 74)	Yes (n = 87)		
Qualitative variables N (%)					
Gender	Male	26 (35.1)	25 (28.7)	51	0.384
	Female	48 (64.9)	62 (71.3)	110	
Marital status	Married	66 (89.2)	81 (93.1)	147	0.384
	Single	8 (10.8)	6 (6.9)	14	
HTN	No	48 (64.9)	64 (73.6)	112	0.232
	Yes	26 (35.1)	23 (26.4)	49	
Cardiac disease	No	66 (89.2)	77 (88.5)	143	0.891
	Yes	8 (10.8)	10 (11.5)	18	
Previous urology surgery	No	63 (85.1)	66 (75.9)	129	0.142
	Yes	11 (14.9)	21 (24.1)	32	
BPH	No	67 (90.5)	75 (86.2)	142	0.396
	Yes	7 (9.5)	12 (13.8)	19	
Quantitative variables (Mean ± SD)					
Age (years)		50.92 ± 7.78	52.09 ± 7.44	51.55 ± 7.59	0.330**
BMI (kg/m²)		28.31 ± 2.21	28.95 ± 2.28	28.65 ± 2.26	0.078**
Diabetes duration (year)		7.45 ± 1.82	7.98 ± 1.79	7.74 ± 1.83	0.069**

UTI: Urinary tract infection, HTN: Hypertension, BPH: benign prostatic hyperplasia, BMI: Body mass index, SD: Standard deviation.
*Chi-square, **Independent T-test.

Table 2. Frequency distribution of clinical data among T2DM patients with and without recurrent UTI

Demographic data		Recurrent UTI		Total	*P* value*
		No (n = 74)	Yes (n = 87)		
Qualitative variables N (%)					
Metformin use	No	13 (17.6)	15 (17.3)	27	0.828
	Yes	61 (82.4)	72 (82.7)	133	
Sitagliptin use	No	34 (45.9)	38 (43.7)	72	0.773
	Yes	40 (54.1)	49 (56.3)	89	
Quantitative variables (Mean ± SD)					
HBA1c		7.34 ± 0.65	7.48 ± 0.58	7.41 ± 0.61	0.162**

UTI: Urinary tract infection, HBA1c: Glycated hemoglobin, SD: Standard deviation. *Chi-square, **Independent T-test.

Table 3. The association of Sitagliptin consumption and occurrence of recurrent UTI using binary logistic regression

Variable			Recurrent UTI occurrence		
			OR	95% CI	*P* value**
Sitagliptin use	Unadjusted	No	Ref (1)		
		Yes	1.09	0.58 – 2.04	0.773
	Adjusted*	No	Ref (1)		
		Yes	1.13	0.57 – 2.23	0.721

UTI: Urinary tract infection, CI: Confidence interval, OR: Odds ratio.
*Adjusted for age, sex, marital status, body mass index (BMI), underlying conditions including cardiac disease and hypertension, duration of diabetes, HbA1c level, history of urological surgery, and benign prostatic hyperplasia (BPH).

drug class might further modulate infectious risk in an already vulnerable population, motivating the present investigation.

The primary finding of the current case-control study, that sitagliptin use was not significantly associated with recurrent UTI in T2DM patients, with an unadjusted OR of 1.09 (95% CI 0.58–2.04, $P = 0.773$) and an adjusted OR of 1.13 (95% CI 0.57–2.23, $P = 0.721$), is strongly consistent with the preponderance of available evidence from clinical trials and observational analyses. In a pooled analysis of safety data from 10,246 patients enrolled across multiple clinical studies, Williams-Herman et al reported nearly identical UTI rates between sitagliptin-exposed and non-exposed groups (23). A subsequent, larger pooled analysis encompassing 14,611 patients across 25 clinical studies corroborated these findings: UTI incidence rates were 4.4 versus 4.8 per 100 patient-years for sitagliptin and comparator arms, respectively, a difference that did not approach statistical significance (24). At the level of the entire DPP-4 inhibitor class, a meta-analysis of randomized controlled trials found an overall infection risk comparable to placebo, with UTI risk specifically showing no meaningful difference between DPP-4 inhibitors and comparators (25). Similarly, a meta-analysis involving 18,980 patients confirmed a Mantel-Haenszel OR for UTI of 0.97 (95% CI 0.70–1.34, $P = 0.83$) for DPP-4 inhibitors versus active comparators (26). A network meta-analysis comparing new oral hypoglycemic agents ranked sitagliptin among the safest agents for UTI risk and found that, as a class, DPP-4 inhibitors demonstrated greater reductions in UTI risk relative to SGLT2 inhibitors and placebo (27). Furthermore, a systematic review and meta-analysis drawing on six large cardiovascular outcome trials encompassing 53,616 patients reported a relative risk of 1.02 (95% CI 0.95–1.10) for UTI among DPP-4 inhibitor users, affirming no heightened infectious risk in real-world clinical practice settings (28). Collectively, the present results extend this body of evidence to a Middle Eastern clinical population with recurrent, rather than incident, UTI as the outcome of interest.

Not all prior evidence points uniformly in the same direction, however, and a measured examination of discordant findings is warranted. A retrospective cohort study conducted in Japanese patients aged 75 years and older identified a statistically significant association between DPP-4 inhibitor use and UTI risk, with an adjusted incidence rate ratio (IRR) of 1.23 (95% CI 1.04–1.45); notably, the signal was particularly pronounced in elderly males with comorbid prostatic hyperplasia (adjusted IRR 2.32, 95% CI 1.40–3.84) (29). Several factors may explain why the current study did not observe analogous findings. First, the age distribution and degree of urological comorbidity in the present cohort, adults seen at a tertiary referral hospital in Tehran, may differ materially from that of a geriatric Japanese registry population, where post-void residual urine from prostatic obstruction substantially amplifies UTI risk independent of pharmacological exposure. Second, the outcome in the present study was recurrent UTI, a more specific endpoint that depends on host susceptibility factors beyond any drug effect alone. Third, from a clinical pharmacology standpoint, sitagliptin does not possess urinary glucose-elevating properties analogous to SGLT2 inhibitors; accordingly, one would not anticipate the substrate-enriched urinary environment that mechanistically links SGLT2 inhibitors to genitourinary infections.

Indeed, understanding why sitagliptin might plausibly be neutral or even mildly protective with respect to UTI requires consideration of the immunological role of DPP-4 itself. DPP-4, the molecular target of sitagliptin, is expressed on a broad array of immune cells, including T lymphocytes (where it is identical to the surface antigen CD26), and participates in the processing of multiple immunomodulatory peptides (19). Inhibition of DPP-4 may therefore exert anti-inflammatory and potentially immunomodulatory effects, which could theoretically attenuate the pro-inflammatory milieu that partly underlies infectious susceptibility in diabetes. Additionally, insofar as sitagliptin improves glycemic control, and elevated HbA1c has been identified as an independent predictor of UTI risk in T2DM, with a hazard ratio of 1.29–1.40 for HbA1c above 9.5% (22), any glucose-lowering benefit might confer indirect protection against infection. At the same time, sitagliptin does not impair renal tubular glucose reabsorption and thus avoids the bacteriuria-promoting glycosuria inherent to SGLT2 inhibitor therapy (27). These considerations are consonant with the null association observed in both the present study and the broader trial literature.

In summary, the findings of the present case–control

study indicate that sitagliptin use is not associated with an increased risk of recurrent UTI in adults with T2DM, with null associations observed in both unadjusted and fully adjusted logistic regression models. These results are consistent with and corroborated by evidence from multiple large-scale meta-analyses and randomized clinical trials (RCTs) demonstrating that DPP-4 inhibitors, including sitagliptin, do not materially elevate overall infection risk or UTI incidence in the general T2DM population. The mechanistic plausibility of a neutral or mildly protective effect is supported by sitagliptin's well-documented anti-inflammatory and immunomodulatory properties, which may offset the heightened infection susceptibility inherent to the hyperglycemic state. A degree of clinical caution is nonetheless warranted in elderly patients with concurrent urological comorbidities such as prostatic hyperplasia, in whom DPP-4 inhibitors may carry a more pronounced UTI risk. From a clinical standpoint, these data support the safety of sitagliptin with respect to UTI recurrence in adult patients with T2DM managed in a hospital outpatient setting, and should reassure clinicians that sitagliptin selection need not be constrained by concerns regarding urinary infection risk in appropriately selected patients. Future prospective studies with larger and more diverse sample sizes, longer follow-up durations, and systematic microbiological documentation of each UTI episode would further clarify the nuanced relationship between DPP-4 inhibitor use and urinary infectious outcomes across different diabetic subpopulations.

Conclusion

This study suggests that sitagliptin use is not associated with an increased risk of recurrent UTI among patients with T2DM, even after accounting for key demographic and clinical confounders, suggesting that this agent appears safe with respect to UTI recurrence in this population. Collectively, these findings imply that recurrent UTI in this population is unlikely to be driven by sitagliptin exposure per se and may instead be more strongly influenced by other, unmeasured or non–drug-related factors.

Limitations of the study

First, the case–control design is inherently susceptible to recall and selection bias, particularly because exposure to sitagliptin and history of recurrent UTI were partly based on patient self-report in addition to medical records. Second, the single-center setting and relatively modest sample size may limit the generalizability of the results and reduce statistical power to detect small to moderate associations. Third, although we adjusted for multiple demographic and clinical confounders, residual confounding from unmeasured factors (Detailed urodynamic parameters, sexual activity, hygiene practices, or prior antibiotic exposure) cannot be excluded. Fourth, the classification of recurrent UTI relied on available documentation and may have been affected by under-diagnosis or incomplete microbiological confirmation, leading to potential outcome misclassification. Finally, the restriction to patients treated with metformin with or without sitagliptin, while reducing confounding by other anti-diabetic drugs, may limit the applicability of the findings to broader therapeutic regimens in routine clinical practice.

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Authors' contribution

Conceptualization: Shabnam Tehrani and Kasra Mardani.
Data curation: Shabnam Tehrani and Kasra Mardani.
Formal analysis: Elmira Mahmoudi Chalmiani.
Investigation: Leila Mahmoudieh, Shabnam Tehrani, and Elmira Mahmoudi Chalmiani.
Methodology: Elmira Mahmoudi Chalmiani and Leila Mahmoudieh.
Project management: Kasra Mardani.
Resources: All authors.
Supervision: All authors.
Validation: Shabnam Tehrani and Leila Mahmoudieh.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki. This study was conducted at Labbafinezhad Hospital in Tehran and is derived from the thesis work of Kasra Mardani (Thesis #43015807), under the ethical code (IR.SBMU.MSP.REC.1404.375), approved by the Shahid Beheshti University of Medical Sciences, Tehran, Iran. Accordingly, informed written consent was obtained from all participants. Furthermore, the authors have fully observed ethical considerations (including plagiarism, data fabrication, and duplicate publication).

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used generative artificial intelligence (Perplexity) and AI-assisted writing tools (Grammarly) to assist with drafting, language editing, and refinement of grammar and style. All content generated by these tools was subsequently critically reviewed, revised, and validated by the authors, who take full responsibility for the accuracy, integrity, and originality of the work.

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