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Association between Simvastatin and Lower Urinary Tract Symptoms: A Cross-Sectional Study in Chronic Disease Management Program Patients in Gorontalo, Indonesia

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Abstrack

Background: Adverse effects associated with simvastatin use have been linked to lower urinary tract symptoms (LUTS), which may negatively impact medication adherence.

Objective: To determine the association between simvastatin use and LUTS among PROLANIS patients in Gorontalo Province, Indonesia.

Methods: A cross-sectional study was conducted among PROLANIS patients residing in rural, peri-urban, and urban areas of Gorontalo Province. Purposive sampling was employed to recruit eligible patients and sites. Simvastatin use was categorized according to duration of therapy (non-users, <6 months, and >6 months). LUTS was assessed using the International Prostate Symptom Score (IPSS) and classified as mild, moderate, or severe. Significant LUTS was defined as an IPSS score ≥8.

Results: Of the 96 participants, 46.9% were regular long-term simvastatin users. Clinically significant LUTS was reported by 28.1% of participants. A positive correlation was observed between the intensity of simvastatin use and LUTS severity (r=0.021, p=0.038). However, no significant difference in the proportion of statin users or LUTS prevalence was found across rural, urban, and peri-urban areas.

Conclusion: Simvastatin use is associated with worsening LUTS. Further studies with larger sample sizes and multi-centre designs are warranted to confirm these findings.

Keywords: Adverse Effects, LUTS, Statin, Urinary Bladder

Introduction

Statins are among the most widely prescribed medications, commonly used to lower LDL cholesterol and for both primary and secondary prevention of cardiovascular disease.[1] Their use increases with age (≥40 years) and in patients at high risk of atherosclerotic cardiovascular disease,[2] underscoring their critical role in the management of cardiovascular emergencies.

Despite their widespread use, statin therapy is limited by adverse effects, which can negatively impact medication adherence.[3] The incidence of statin-related side effects may reach up to 30%, with statin-associated muscle symptoms (SAMSs) being the most frequently reported.[4,5] Other documented adverse effects include new-onset type 2 diabetes mellitus, neurocognitive effects, hepatotoxicity, and renal toxicity, among others.[6] However, the precise mechanisms underlying these effects remain incompletely understood.

In the urogenital system, statin use has been associated with interstitial cystitis, a condition that presents with lower urinary tract symptoms (LUTS), including dysuria, urinary frequency, and urgency, which can significantly impair patients' quality of life.[7] The global burden of clinically significant LUTS among statin users remains poorly characterized. A retrospective study conducted in the United States by St. Sauver et al. among men aged over 40 years demonstrated an increasing trend in moderate-to-severe LUTS from 1990 to 2007, with incidence rates rising from 5% to 40% by the end of the observation period. However, in the same study, the incidence rate was significantly lower than that observed in non-statin users.[8] Another study by Hall et al., involving 5,503 participants, reported a prevalence of clinically significant LUTS of 20.2% and 23.4% among male and female statin users, respectively. No significant difference in LUTS prevalence was found between statin users and non-users.[9] In Indonesia, no studies have yet reported the prevalence or incidence of LUTS among statin users. A study by Ibrahim and Hasanuddin in 2024 reported that 38.5% of participants in the Chronic Disease Management Program (Program Pengelolaan Penyakit Kronis, PROLANIS) experienced clinically significant LUTS.[10] Participants in this program generally receive medications for chronic conditions, including statins.[11]

The relationship between statin use and LUTS has yielded conflicting results across studies. A population-based case-control study reported a significant association between regular statin use and LUTS, with an odds ratio of 1.58.[7] In contrast, other studies have suggested a beneficial effect of statins on LUTS, particularly in men with benign prostatic hyperplasia (BPH).[12] Furthermore, some evidence indicates that hydrophilic statins improve overall LUTS in older men, but no similar association has been observed in hydrophobic statins.[13] All existing studies examining the relationship between these two variables have been conducted outside the Southeast Asian region. Given that LUTS prevalence varies across regions,[14] research conducted in Indonesia is needed to confirm the pattern of association between statin use and LUTS in this region.

PROLANIS is an integrated, proactive healthcare service system involving BPJS Health participants.[11] PROLANIS patients were selected as the study population because they have documented chronic conditions, including cardiovascular disease and hyperlipidemia, which are frequently managed with simvastatin. This study aimed to investigate the association between simvastatin use and LUTS among PROLANIS patients in Gorontalo Province. To achieve this,

we recruited participants from representative primary health centers reflecting rural, peri-urban, and urban characteristics.

Methods

This study employed a cross-sectional design conducted at three distinct Primary Health Centers in Gorontalo Province, selected to represent rural (Bulango Ulu), peri-urban (Kabila), and urban (Kota Tengah) characteristics. Data collection was carried out from July to October 2023. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Health Research Ethics Committee of Universitas Negeri Gorontalo on August 30, 2023 (Approval No. 84A/UN47.B7/KE/2023). Written informed consent was obtained from all participants prior to enrollment in the study.

The study population comprised all PROLANIS patients attending these three health centers from 2022 onward. A purposive sampling technique was used. Inclusion criteria were: all PROLANIS patients receiving care at the three health centers, those who had been on controlled simvastatin therapy for at least two months, and those not taking simvastatin. Patients who had discontinued care at these centers, had died, had evidence of urinary tract infection, or were taking diuretic agents were excluded from the study. The minimum sample size was calculated using Slovin's formula. With a population of 150 and a confidence level of 95%, the minimum sample size is 93.

The independent variable was duration and intensity of simvastatin therapy, while the dependent variable was LUTS significant symptoms and severity. Data on simvastatin use were obtained from medical records of PROLANIS patients attending the three health centers, including treatment duration and adherence. Duration of use was dichotomized into long-term routine use (defined as daily consumption for more than six months) and non-long-term use, as a statin therapy duration exceeding six months has been previously associated with LUTS.[12] This binary classification was employed for cross-tabulation analyses against clinically significant LUTS. Conversely, the intensity of simvastatin use was stratified into four ordinal categories based on the reported timeline of statin-related adverse effects from previous studies: non-user, low-intensity (<2 months), moderate-intensity (2–6 months), and high-intensity (>6 months).[15,16] This grouping was utilized in the correlation analysis with LUTS severity.

LUTS was assessed using the Indonesian version of the International Prostate Symptom Score (IPSS), which had been previously validated by Monoarfa and Mochtar.[17] The use of the IPSS score had been validated for assessing LUTS in the general population, including women.[18,19] Questionnaires were administered through direct visits, with researchers accompanying respondents during completion. Participants were classified as having significant LUTS if their IPSS score was ≥8. On the one hand, the categorization of IPSS measurement results also classifies LUTS based on symptom severity: absent (score 0), mild symptoms (score 1–7), moderate symptoms (score 8–19), and severe symptoms (score 20–35).

After data collection, statistical analyses were performed using SPSS version 13.0 for Windows (IBM, USA). Duration of simvastatin use and LUTS severity were expressed as percentages within each category. The correlation between the two variables was analyzed using Spearman's rank correlation test to determine significance, direction, and strength of association.

A p-value <0.05 was considered statistically significant. Correlation direction was determined by the sign (+/-) of the correlation coefficient. Strength of correlation was categorized as: very strong (0.8–1.00), strong (0.6–0.79), moderate (0.4–0.59), weak (0.2–0.39), and very weak (0.0–0.19). In addition, the Chi-square test was used to compare the proportions of simvastatin users and LUTS prevalence across the three health center regions.

Results

The study was conducted at three Primary Health Centers in Gorontalo Province representing urban (Puskesmas Kota Tengah), peri-urban (Puskesmas Kabila), and rural (Puskesmas Bulango Ulu) areas. Initial screening identified 132 participants meeting the inclusion criteria, comprising 41 from Kota Tengah, 65 from Kabila, and 26 from Bulango Ulu. During questionnaire administration, 12 participants did not complete the questionnaire fully. During data validation, an additional 24 participants were excluded due to a history of diseases or medications associated with LUTS. Ultimately, data from 96 participants were analyzed, consisting of 18 from Kota Tengah, 59 from Kabila, and 19 from Bulango Ulu.

The general characteristics of the study participants are presented in Table 1. The majority of participants were from peri-urban areas, were female, and had primary school education or equivalent. The mean age of participants was 59 years, with a range of 28 to 79 years. The proportion of patients who were regular long-term simvastatin users was 46.9%. The majority of participants were classified as high-intensity simvastatin users, followed by non-users and moderate-intensity users. Clinically significant LUTS (IPSS score ≥8) was reported by 28.1% of participants, with the majority having mild symptoms, followed by moderate and severe symptoms.

Table 1. General Characteristics of Participants (N=96)

Parameter	Frequency (n)	Percentage (%)
Origin of Puskesmas		
Kota Tengah (Urban Area)	18	18.80
Kabila (Periurban Area)	59	61.50
Bulango Ulu (Rural Area)	19	19.80
Gender		
Male	16	16.70
Female	80	83.30
Education level		
Elementary School	36	37.50
Junior High School	16	16.70
Senior High School	29	30.20
Higher Education	15	15.60
Age (years)[a]	59.47 ± 10.76	
Long term routine use of Simvastatin		
Yes	45	46.90
No	51	53.10
Intensity of Simvastatin use		
None user	24	25.00
Low	13	13.50
Moderate	14	14.60
High	45	46.90
Significant LUTS		
Present	27	28.10
Absent	69	71.90
LUTS severity		
Absent	5	5.20
Mild	64	66.70
Moderate	21	21.90
Severe	6	6.20

[a]*Mean±standard deviation*

The characteristics of LUTS scoring for each individual symptom are presented in Table 2. The median total IPSS score in this study was 5, with a range of 0 to 27. The majority of participants scored 0 on all symptom categories, except for nocturia. For nocturia, the majority of participants had a score of 1, followed by scores of 2, 3, and 0. The quality of life score related to LUTS among PROLANIS patients had a median of 2, ranging from 0 to 6.

Table 2. Detailed Characteristics of LUTS in the Study Participants (N=96)

IPSS Parameter	Score 0		Score 1		Score 2		Score 3		Score 4		Score 5	
	n	%	n	%	n	%	n	%	n	%	n	%
Total Score[a]	5 (0-27)											
Score at Each Symptom												
Incomplete emptying	56	58.30	10	10.40	2	2.10	16	16.70	3	3.10	9	9.40
Urinary frequency	30	31.20	25	26.00	4	4.20	21	21.90	9	9.40	7	7.30
Urinary intermittency	72	75.00	5	5.20	6	6.20	8	8.30	2	2.10	3	3.10
Urinary urgency	79	82.30	2	2.10	6	6.20	6	6.20	0	0.00	3	3.10
Weak stream	75	78.10	7	7.30	4	4.20	7	7.30	2	2.10	1	1.00
Straining	78	81.20	4	4.20	4	4.20	7	7.30	1	1.00	2	2.10
Nocturia	18	18.80	27	28.10	20	20.80	18	18.80	5	5.20	8	8.30
Quality of life scores[a]	2 (0-6)											

[a]*Median (Min-Max)*

Differences in demographic characteristics based on simvastatin use and significant LUTS are shown in Table 3. Both simvastatin users and non-users had similar characteristics in terms of region of origin, sex, educational level, and age. Furthermore, participants with and without significant LUTS were comparable in terms of region of origin, sex, educational level, and age.

Table 3. Demographic Characteristics Based on Simvastatin Consumption and LUTS Positivity Among Study Participants (N=96)

Characteristics	Long term routine use of Simvastatin		p-value	Significant LUTS Symptoms		p-value
	Yes (n=45)	No (n=51)		Yes (n=27)	No (n=69)	
	n (%)	n (%)		n (%)	n (%)	
Origin of Puskesmas						
Kota Tengah (Urban Area)	6 (13.30)	12 (23.50)	0.323[b]	6(22.20)	12(17.40)	0.753[b]
Kabila (Periruban Area)	31(68.90)	28(54.90)		15(55.60)	44(63.80)	
Bulango Ulu (Rural Area)	8 (17.80)	11(21.60)		6(22.20)	13(18.80)	
Gender						
Male	8(17.80)	8(15.70)	0.784[b]	2(7.40)	14(20.30)	0.221[d]
Female	37(82.20)	43(84.30)		25(92.60)	55(79.70)	
Education Level						
Elementary School	18 (40.00)	18(35.30)	0.848[b]	12(44.40)	24(34.80)	0.467[d]
Junior High School	7(15.60)	9(17.60)		5(18.50)	11(15.90)	
Senior High School	12(26.70)	17(33.30)		5(18.50)	24(34.80)	
Higher Education	8(17.80)	7(13.70)		5(18.50)	10(14.50)	
Age (years)[a]	62 (28-78)	58 (37-79)	0.956[c]	62 (28-78)	58 (37-79)	0.903[c]

[a]*Median (Min-Max)* [b]*Chi-Square test* [c]*Mann-Whitney test* [d]*Fisher-Exact test*

The association between simvastatin use and significant LUTS is shown in Table 4. The majority of regular long-term simvastatin users did not experience significant LUTS. Similarly, most participants who were not regular long-term simvastatin users also did not have significant LUTS. No significant association was found between simvastatin use and significant LUTS in this study (p = 0.128).

Table 4. The Relationship between Duration of Simvastatin Use and Significant LUTS (N=96)

Long term routine use of Simvastatin	Significant LUTS				Total	Percentage	p-value
	Yes		No				
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)			
Yes	16	40.70	29	42.00	45	46.90	0.128[a]
No	11	59.30	40	58.00	51	53.10	
Total	**27**	**28.10**	**69**	**71.90**			

[a]*Chi-Square test*

The correlation between the intensity of simvastatin use and LUTS severity is presented in Table 5. Intensity of simvastatin use was weakly positively correlated with LUTS severity (ρ = 0.212; p = 0.038). The coefficient of determination (R^2) was 0.045, indicating that 4.5% of the variance in LUTS severity could be explained by the intensity of simvastatin use, while the

remaining 95.5% was attributable to other unexamined factors. In contrast, no significant correlation was found between the intensity of simvastatin use and total IPSS score or its individual symptom scores. However, a positive correlation was observed between the intensity of simvastatin use and quality of life score ($\rho = 0.277$; $p = 0.006$), with an R^2 of 0.077, indicating that 7.7% of the variance in patients' quality of life was explained by the intensity of simvastatin use, while the remaining 92.3% was determined by other factors not investigated in this study.

Table 5. Correlation between Simvastatin Usage Intensity and LUTS Symptoms

LUTS Parameter	ρ	R^2	p-value[a]
LUTS Severity	0.212	0.045	0.038*
LUTS Subdomain Score	0.193	0.037	0.059
Incomplete emptying	0.086	0.007	0.404
Urinary frequency	0.183	0.033	0.074
Urinary intermittency	0.152	0.023	0.139
Urinary urgency	-0.010	0.000	0.924
Weak stream	0.118	0.014	0.251
Straining	0.175	0.031	0.089
Nocturia	0.183	0.033	0.074
Quality of life score[a]	0.277	0.077	0.006*

[a]*Spearman-Rank Correlation Test* *Significant at p<0.05*

Discussion

The occurrence of statin-related adverse effects may be influenced by the level of medication adherence, as the initiator of the present study.[20] In this study, the majority of PROLANIS patients were non-users of simvastatin, although the proportion did not differ substantially from that of users. This finding diverges from earlier reports indicating that simvastatin is commonly prescribed in PROLANIS populations for the prevention and management of hyperlipidemia, a condition that may promote cholesterol deposition in arterial walls, vascular narrowing, and elevated blood pressure—all of which are risk factors for heart disease and stroke.[21–23] This discrepancy may be attributable to the relatively stringent criteria used to define simvastatin use in our study, which required regular consumption over a period exceeding six months. Different estimates might have emerged had we used a simpler binary classification (ever vs. never used) without considering regularity and duration of therapy.

The prevalence of clinically significant LUTS in this study was 28.1%, which is lower than the global prevalence of 31.3%.[14] This similarity may reflect the multifactorial nature of LUTS, which can be influenced by medication use, age, sex, and various comorbidities.[24] In our study, several participants with conditions or concurrent medications that could affect LUTS were excluded, thereby potentially reducing the likelihood that any observed symptoms were related to simvastatin use. Another factor that may account for this prevalence discrepancy is the gender distribution. Women comprised a substantially larger proportion of the sample than men in this study, whereas LUTS is generally more prevalent in males.[14]

The relationship between statin use and LUTS has yielded conflicting results across studies. In the present study, we did not find a statistically significant association between regular long-term simvastatin use and clinically significant LUTS. A population-based case-control study in Taiwan reported a significant association between regular statin use and significant LUTS, with the study population being predominantly female and diagnosed with interstitial cystitis.[7]

In contrast, other studies have suggested a beneficial effect of statins on LUTS, particularly in men with benign prostatic hyperplasia (BPH).[12] Upon closer examination, these studies differ substantially in their sample characteristics. Statins tend to exacerbate LUTS in female populations or in males without pre-existing benign prostatic enlargement (BPE). Conversely, statins appear to exert a positive effect in improving LUTS among male populations, especially those with pre-existing BPE.

A secondary analysis revealed a weak but positive correlation between the intensity of simvastatin use and the severity of LUTS. The weak correlation between these two variables suggests that LUTS severity may be more closely associated with other unexamined factors, such as chronic comorbidities and psychological factors.[25] Nevertheless, this study may serve as an important foundation for monitoring LUTS in patients who have been on long-term, intensive statin therapy.

The existence of a link between simvastatin and LUTS is supported by previous research proposing three potential mechanisms by which statins may contribute to storage-phase LUTS. First, statins may interfere with serotonergic neurotransmission by reducing cholesterol availability, which is essential for lipid raft formation that anchors receptors and signaling proteins, potentially leading to affective disturbances implicated in storage symptoms. Second, statins may inhibit cerebral cholesterol biosynthesis, thereby affecting synaptic cholesterol homeostasis and central myelination. Inadequate myelin production could result in demyelination of central nervous system fibers, which is hypothesized to underlie storage-phase LUTS. Third, statins may reduce serum cholesterol levels, which in turn may affect aldosterone concentrations, potentially leading to increased urinary frequency.[13]

The relationship between statins and LUTS has also been explored in previous investigations. One study suggested that statins may disrupt the uroepithelial lining of the urinary bladder, which is a primary contributor to bladder pain syndrome/interstitial cystitis (BPS/IC), a condition characterized by LUTS.[26] Moreover, statins may impair uroepithelial cell proliferation by influencing stem cell activity, potentially promoting cellular senescence through upregulation of p16 and p53.[27,28] Senescent cells are known to elicit chronic inflammatory responses by secreting pro-inflammatory cytokines, proteinases, and growth factors. This chronic inflammation is a known driver of LUTS.[29,30]

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes the establishment of a causal relationship between simvastatin use and LUTS, as it captures only a single point in time. Second, the relatively small sample size (n=96) may limit the statistical power to detect smaller, yet clinically meaningful, differences, and the purposive sampling method may introduce selection bias, thereby limiting the generalisability of the findings to the broader PROLANIS population. Third, LUTS assessment relied solely on the self-reported IPSS questionnaire, which is subjective and may be influenced by recall bias or patients' perception of their symptoms; objective measures such as urodynamic studies were not performed. The measurement of LUTS using the IPSS in women has been validated to yield results similar to those in men; however, it lacks specificity for female-specific conditions such as incontinence.[31] Fourth, no multivariable adjustment was performed. Potential confounding factors—including comorbidities (e.g., benign prostatic hyperplasia, diabetes mellitus),

concomitant medications, lifestyle factors (smoking, alcohol consumption), and duration of statin therapy—were not fully controlled for, which may have influenced the observed association. Fifth, the study was conducted in a single province and may not reflect the diversity of other regions in Indonesia. Despite these limitations, the findings provide preliminary evidence that warrants further investigation through larger, prospective, multi-centre studies with longer follow-up to confirm the association and elucidate the underlying mechanisms.

Conclusion

Regular, long-term simvastatin use among PROLANIS participants was relatively low, and a notable proportion of the study population experienced clinically significant LUTS. In general, there is no significant association between duration of statin use and significant LUTS symptoms. However, higher intensity of simvastatin use may be subtly related to advanced LUTS severity, particularly with respect to the health-related quality of life impacted by these symptoms. Geographic location did not appear to influence LUTS prevalence or simvastatin use patterns among PROLANIS patients. Further studies with larger, multicenter cohorts are warranted to confirm the association observed in this investigation.

Conflict of Interest

Nothing to declare.

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