Received: 24 February 2024 | Revised: 30 March 2024 | Accepted: 03 April 2024
DOI: 10.48309/JMPCR.2024.445490.1131
Journal of Medicinal and Pharmaceutical Chemistry Research
SAMI

FULL PAPER

Analysis of lower urinary tract symptoms (LUTS) in diabetes mellitus type 2 (DM2) patients at an indonesian primary health care: A cross-sectional study

Noka Yogahutama[a,*] |Muhammad Rifqi Ulil Abshor[b] |Muhammad Isa Fuad Affan[c]

[a]*Rembang II Primary Health Care, Rembang, Indonesia*

[b]*Emergency Department, Dr. R. Soetrasno Hospital, Rembang, Indonesia*

[c]*Urology Department, Dr. R. Soetrasno Hospital, Rembang, Indonesia*

***Corresponding Author:**
Noka Yogahutama
Email: nokahutama@ymail.com
Tel.: +6282328811782

Lower Urinary Tract Symptoms (LUTS) commonly develop in patients with Type 2 Diabetes Mellitus (DM2). The prevalence rate of LUTS among DM2 patients in Indonesia remains uncertain. However, more than half of LUTS patients could be treated conservatively, making it suitable for management in Primary Health Care (PHC). This study aims to describe the prevalence rate of LUTS, and related factors associated with the presence of LUTS among DM2 patients. This study was conducted at PHC in Rembang city, Central Java, Indonesia. Over 3 months, data were collected from a total of 131 male and female DM2 patients with questionnaires consisting of sociodemographic characteristics, clinical and laboratory examination results, and International Prostate Symptoms Score in Indonesian language (IPSS-Ina). Prevalence Ratio (PR) calculation and Chi-Square Test were performed. Adjustment of PR value with regular amlodipine consumption in the past month factor resulted in adjusted PR (aPR) value. P-value less than 0.05 was considered statistically significant. The LUTS prevalence among 131 DM2 subjects was 75.57%. LUTS was significantly associated with age (p = 0.002), hyperglycemia (p = <0.001), duration of DM2 diagnosis (p = 0.006), amlodipine consumption in the past 1 month (p = <0.001), and parity amount (female) (p = 0.015). Advanced age, hyperglycemia, duration of DM2 diagnosis, regular amlodipine consumption in the past month, and higher parity (female) increased the risk of LUTS in DM2 patients.

KEYWORDS

LUTS; DM2; IPSS; prevalence; urinary symptoms.

Introduction

The global population of Diabetes Mellitus (DM) has exceeded 10 million, and Indonesia is among the top ten countries with the highest DM population [1]. Approximately 90-95% of the entire DM population consists of DM2 patients [2]. In 2018, the prevalence rate of DM in Indonesia was approximately 8.5% [3]. The prevalence of DM is increasing every year due to modernization and urbanization, leading to lifestyle changes that contribute to a high disease burden, especially in Low Middle Income Countries (LMICs) especially Indonesia [4]. DM Complication manifests in macrovascular complications such as

cardiovascular disease, stroke, peripheral vascular disease, and microvascular complications such as neuropathy, nephropathy, and retinopathy [5]. These diabetic complications may exacerbate or cause LUTS, which are common symptoms in diabetic patients [6]. Even increased frequency (Polyuria), as one of the LUTS, becomes one of the earliest classic symptoms of diabetes [7]. Mechanisms of LUTS in DM have been investigated in a few studies, such as the exacerbation of Benign Prostate Hyperplasia (BPH) in DM and autonomic neuropathy affecting the detrusor muscle and urothelium, leading to Lower Urinary Tract Dysfunction (LUTD), and even Urinary Tract Infections (UTIs) [8-10]. Identifying specific types of LUTS in DM may provide insights into underlying pathologies.

LUTS is an umbrella term that consists of storage symptoms, voiding symptoms, and post-voiding symptoms, covering any symptoms associated with the function of the lower urinary tract [10]. The main problem with LUTS is the discomfort it causes, leading to various morbidities. This issue has been shown to negatively affect the Quality of Life (QoL). LUTS is associated with increased rates of anxiety and depression, and has an impact on work productivity, enjoyment of sexual activity, and overall health [11]. Globally, the prevalence rate of LUTS ranges from 15.8 to 82.0% in the adult population [12]. The wide range of variation in LUTS prevalence rates is due to differences in the LUTS definition, with many studies focusing on specific types of LUTS such as Urinary Incontinence (UI), or symptoms associated with specific diseases such as Benign Prostate Hyperplasia (BPH), Overactive Bladder (OAB), or only focusing on specific genders or populations, especially in Western populations [12]. In 2015, a study conducted in China with 3023 participants of both genders showed a prevalence rate of 61.2% among the participants [12]. In Indonesia, most studies of LUTS have focused only on male patients with BPH. In 2016, a study focused on UI with 2765 participants of both genders showed a prevalence rate of 13.0% [13]. To date, there has been no study focused on the prevalence rate of LUTS in the diabetic population, especially in Indonesia. Few studies have stated LUTS risk factors, with advanced age being one of the most significant [12,14]. A study in 2022 with 378 Palestinian primary care diabetic participants showed that BMI and regular exercise were the most significant factors associated with LUTS severity [6]. In addition, this study stated that diabetic participants using a combination of medication and insulin tended to have LUTS, reflecting uncontrolled DM, and the DM duration tended to have a positive correlation with LUTS [6]. The true burden of LUTS may be underestimated due to under-reporting. Patients with LUTS tend to not report any symptoms until they significantly affect their daily activities. This is caused by a stigma, especially among the Indonesian population, that LUTS is a normal condition associated with aging. However, the association between DM and LUTS has not been completely understood and needs further studies.

In a clinical setting, LUTS could not be a definitive diagnosis. Each specific symptom of LUTS may reflect a specific underlying etiology. Although there is a wide variety of LUTS etiologies, the management and therapies for LUTS are still uncertain, especially in primary care settings. The National Institute for Health and Clinical Excellence (NICE) guidelines stated that many men referred to specialist care with LUTS are eventually managed conservatively, and thus they could have remained within primary care [15]. In addition, most males presenting with LUTS could be effectively treated in primary care [11]. Primary care should serve as a gate to screening LUTS, and General Practitioners (GPs) in primary care should be able to determine the severity of LUTS and establish LUTS referral criteria. To date, there is no basic guideline and management of LUTS in primary care settings in Indonesia. This study was aimed to describe the prevalence rate of

LUTS, and related factors associated with the presence of LUTS among DM2 patients. We hope that the results of this study could provide a better understanding of LUTS and DM2 in Indonesia and serve as a reflection for policymakers to develop nationally standardized strategies and tools for primary care in preventing and reducing the prevalence of LUTS, especially in DM2 patients.

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Experimental

A cross-sectional study was conducted to assess the prevalence of LUTS and its related factors among patients with DM2. A modified questionnaire was used to collect data from the participants. The questionnaire was administered in two outpatient clinics of Rembang II PHC owned by Rembang Health Office located in Rembang District, Central Java Province, Indonesia. The target population was all DM2 patients that routinely controlled their treatment in Rembang II PHC. All data were collected between April 2023 and June 2023. All data were obtained during Rembang II PHC operational days and hours (Monday to Saturday, from 8 a.m. to 12 p.m.). All patients (18 years old or older) who were diagnosed with DM2 and confirmed to have DM2 through laboratory tests were included. All included patients were registered in two outpatient clinics of Rembang II PHC during the study period and provided written informed consent. Patients who did not sign the written informed consent or had any established diagnosis of urogenital conditions, a history of urological surgery or recurrent UTIs, or those with psychiatric diseases were excluded. This study has been approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University, Indonesia (310/UN1/FK-KMK.3/PK.2/TL/2023). Written and verbal consent were obtained from all participants before collecting the data.

The sample size was calculated based on the formula for cross sectional study with qualitative variables [16]. At least 49 participants were enrolled with margin of error at 5% and confidence interval at 95%. The consecutive sampling was used, and indeed a total of 131 participants were obtained during the study period.

A questionnaire in Indonesian language was used, which consisted of three sections: sociodemographic characteristics, laboratory and physical examination results, and the standardized IPSS in Indonesian language (IPSS-Ina). In the sociodemographic characteristics section (first section), we gathered information on age, gender, address, education level, alcohol consumption rate, smoking status, occupation, monthly income, number of partners, parity (only for females), sexual activity, duration of DM2 diagnosis, other morbidities, and type and dosage of DM2 and hypertension medication taken in the past month. The laboratory and physical examination results section (second section) included Body Mass Index (BMI), blood pressure level, and blood glucose level. BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2) based on height (cm) and weight (kg) measurements. Blood pressure levels were measured using a standardized and calibrated automatic sphygmomanometer, providing systolic and diastolic pressures (mmHg). Blood glucose levels were examined using standardized and calibrated laboratory test kits, with samples taken from the patient's vein for plasma glucose measurement. This included Fasting Plasma Glucose (FPG), Two-Hour Plasma Glucose (2-hour Postprandial Glucose), or Random Blood Glucose (RBG), following the guidelines outlined in the "Guidelines for the Management and Prevention of Type 2 Diabetes Mellitus in Adults in Indonesia 2021" by the Indonesian Association of Endocrinologists (PERKENI) [7]. The first and the second sections were

administered and examined by qualified GPs. The third section contained the standardized IPSS in Indonesian language, known as IPSS-Ina. This section was retrieved from the "Clinical Management of Benign Prostatic Hyperplasia (BPH), 4th ed" published by the Indonesian Association of Urologists [17]. IPSS was a self-administered questionnaire completed by the participants, consisting of seven questions related to symptomatic frequency and one question related to QoL. This questionnaire was selected for our study by considering the briefness of the questionnaire, the educational level of the subjects, and its simplicity in screening LUTS. In addition, the IPSS has been widely used in Indonesia as the primary tool for assessing the severity of LUTS. Although originally designed to evaluate LUTS associated with BPH in males, several studies have shown that IPSS is a valid and reliable tool for evaluating LUTS in females due to other causes [18-20]. Three of the seven symptomatic frequency questions were associated with storage symptoms (Q2: Frequency, Q4: Urgency, and Q7: Nocturia), while the remaining questions were related to voiding symptoms (Q1: Incomplete emptying, Q3: Intermittency, Q5: Weak stream, and Q6: Straining) [21]. Each of the seven symptomatic frequency questions had a scale ranging from zero (Not at all) to five (Almost always). The total score of these seven questions was interpreted based on a previous study, classifying scores as follows: LUTS absent (0), and LUTS present (>=1).[14] LUTS present category can be further classified based on the LUTS severity: mild (1-7), moderate (8-19), and severe (20-35) [14].

All the data were entered and organized in Microsoft Excel 2017. Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0. The LUTS prevalence was calculated and presented as proportions. The IPSS-Ina total scores, sociodemographic characteristics, and laboratory and physical examination results were presented and grouped as categorical variables. To test the association between IPSS-Ina total scores and sociodemographic characteristics, as well as laboratory and physical examination results, we performed the Chi-Square Test. Fisher's Exact Test was performed for variables with an expected cell count below 5 in the Chi-Square Test. A p-value below 0.05 was considered statistically significant. PR with 95% Confidence Intervals (95% CIs) were used to measure the association between variables. Binary logistic regression was used to estimate PR. This model was also used to adjust the PR according to regular amlodipine consumption in the past month variable, the results were presented in aPR. A PR value higher than 1 indicated a positive association, while a PR value below 1 indicated a negative association.

Results

Subject characteristics

A total of 131 subjects diagnosed with DM2 were recruited for this study, with characteristics indicated in Table 1. Among them, 41 subjects (31.30%) were aged 60 or older, while 90 subjects (68.70%) were aged below 60 years old. Nearly one-third of the subjects were female, with 94 subjects (71.76%), while male subjects accounted for 37 subjects (28.24%). The majority of male subjects (32.43%) were included in the age group of 60-69 years old with a mean age of 57.27±11.71 years and the oldest subject was 86 years old. Among the female subjects, most of them (43.62%) were in the age group of 50-59 years old, with a mean age of 54.67±8.62 years, and the oldest subject was 76 years old. Most of the subjects (75.57%) had graduated from elementary school or had a lower level of education. In addition, out of the 71 subjects (54.20%) who were employed, only 30 of them had a monthly income of 2 million Rupiah or higher. All 22 subjects who were active smokers were male, while only 2 subjects (1.53%), consisting of one male and one female subject ever consumed alcohol.

Most of the subjects were married, and 70 subjects (53.44%) reported having regular sexual activity or having at least one sexual activity in the past month. All of the female subjects had at least one child. Out of the 94 female subjects, 52 subjects (55.32%) had between one or two children, while 42 subjects (44.68%) had three or more children. The majority of these parities were through vaginal delivery.

A total of 89 subjects (67.94%) were diagnosed with DM2 within the past five years. The majority of subjects (98 subjects or 74.81%) fell under the criteria of hyperglycemia or uncontrolled DM, as defined by the "Guidelines for the Management and Prevention of Type 2 Diabetes Mellitus in Adults in Indonesia 2021" issued by the Indonesian Association of Endocrinologists (PERKENI) [7]. It is important to note that all participants were regularly consuming individual or combined DM medications available at Rembang II PHC, including metformin, glibenclamide, and glimepiride. During physical examination, approximately three-fourths of all subjects (73.28%) had a normal or underweight BMI. Merely 35 subjects (26.72%) had an overweight BMI. Similarly, during the examination, 103 subjects (78.63%) had blood pressure that met the criteria for hypertension. However, not all of them were diagnosed with hypertension or regularly took hypertension medication before the examination. Only 70 subjects (53.44%) out of the 131 subjects had been diagnosed with hypertension before the examination and regularly took individual or combined hypertension medication in the past month. There were only two hypertension medications available in Rembang II PHC, which is amlodipine and captopril. Among these 70 subjects, 57 subjects (81.42%) were regularly taking amlodipine in the past month.

TABLE 1 Characteristic of subjects

Characteristics	n (%)
Age	
Age >=60	41 (31.3)
Age <60	90 (68.7)
Sex	
Male	37 (28.24)
Female	94 (71.76)
Overweight	
Yes	35 (26.72)
No	96 (73.28)
Hypertension	
Yes	103 (78.63)
No	28 (21.37)
Hyperglycemia	
Yes	98 (74.81)
No	33 (25.19)
Education level	
Elementary school or lower	99 (75.57)
Higher than elementary school	32 (24.43)
Alcohol consumption	
Ever consumed	2 (1.53)
Never consumed	129 (98.47)
Smoking status	

Active smoker	22 (16.79)
Non-smoker or former smoker	109 (83.21)
Occupation	
Unemployed	60 (45.8)
Employed	71 (54.2)
Monthly income	
< IDR 2000k	101 (77.1)
>= IDR 2000k	30 (22.9)
Sexual activity	
Regular or at least once in the past month	70 (53.44)
Never or no sexual activity in the past month	61 (46.56)
DM2 diagnosis duration	
>=5 year	42 (32.06)
<5 year	89 (67.94)
Regular hypertension drug consumption (1 month)	
Yes	70 (53.44)
No	61 (46.56)
Regular amlodipine consumption (1 month)	
Yes	57 (43.51)
No	74 (56.49)
Parity (Female)	
>=3	42 (44.68)
<3	52 (55.32)

LUTS Prevalence

The LUTS prevalence in DM2 presented in Table 2 was 75.57% for both genders, specifically 81.08% in male subjects and 73.40% in female subjects. These results were obtained from any subjects included in LUTS present category (IPSS >=1) compared to all subjects. Among 99 subjects with LUTS, 62 subjects (62.63%) had mild LUTS, 32 subjects (32.32%) had moderate LUTS, and 5 subjects (5.05%) had severe LUTS. The mean total IPSS was 4.97±4.85, with 6.19±6.25 in male subjects and 4.49±4.11 in female subjects. The highest total IPSS recorded was 22, while the highest total IPSS in female subjects was 20. Both male and female subjects with moderate LUTS had slightly different prevalences, ranging from 30.00% to 33.33%. However, there were more male subjects with severe LUTS compared to female subjects.

TABLE 2 LUTS prevalence and severity

LUTS Prevalence			
	Total (n= 131)	Male (n= 37)	Female (n= 94)
	n (%)	n (%)	n (%)
LUTS Present (IPSS >=1)	99 (75.57)	30 (81.08)	69 (73.4)
LUTS Absent (IPSS 0)	32 (24.43)	7 (18.92)	25 (26.6)
LUTS Severity			
	Total (n= 99)	Male (n= 30)	Female (n= 69)
	n (%)	n (%)	n (%)
Mild (1-7)	62 (62.63)	17 (56.67)	45 (65.22)
Moderate (8-19)	32 (32.32)	9 (30)	23 (33.33)
Severe (20-35)	5 (5.05)	4 (13.33)	1 (1.45)

Characteristics associated with LUTS

The number of subjects with LUTS was higher compared to subjects without LUTS. As a proportion, subjects with LUTS were more common in every category, as provided in Table 3. There was a statistically significant association between LUTS and age, hyperglycemia, DM2 diagnosis duration, and regular amlodipine consumption in the past month. The proportion of subjects aged 60 or older was smaller than that of subjects aged lower than 60 (31.3% vs. 68.7%), as shown in Table 1. However, subjects aged 60 or older showed a positive association with LUTS as indicated by p-value (0.002) and PR value 1.36 (95% CI 1.15-1.61). Even after adjusting for regular amlodipine consumption in the past month, the association remained stronger with aPR value of 3.05 (95% CI 2.59-3.61).

Hyperglycemia showed a strong association with LUTS as indicated by P-value of <0.001. As shown in Table 1, the proportion of hyperglycemia was 74.81%, as listed in Table 3, 87 subjects (88.78%) among those subjects had LUTS. Subjects with hyperglycemia had a 2.44 times higher chance of developing LUTS compared to subjects without hyperglycemia. Furthermore, among the subjects with hyperglycemia, those who regularly consumed amlodipine in the past month had a 5.46 times higher chance of developing LUTS, as shown by aPR value in Table 3. The duration of DM2 diagnosis also showed an association with LUTS, as shown by statistically significant P-value of 0.006. Subjects who were diagnosed DM2 in 5 years or more had a 32% higher chance of developing LUTS as reflected by the PR value of 1.32 (95% CI 1.11-1.56). The chance was doubled with adjustment of regular amlodipine consumption in the past month, as reflected by aPR value of 2.95 (95% CI 2.48-3.5). Out of 70 subjects who were diagnosed with hypertension and regularly consumed hypertension drugs in the past month, 57 subjects (81.42%) were regularly consuming amlodipine in the past month, as shown in Table 1. According to the statement above, regular amlodipine consumption and LUTS had a statistically significant association with a p-value <0.001, as shown in Table 3.

On the other hand, regular hypertension drug consumption (Consist of amlodipine and/or captopril) in the past month did not show a statistically significant association with LUTS, with a p-value of 0.713. Furthermore, regular hypertension drug consumption in the past month and LUTS had a slightly negative association with a PR value of 0.96 (95% CI 0.79-1.17) compared to regular amlodipine consumption in the past month and LUTS positive association with a PR value of 1.43 (95% CI 1.18-1.73). The amount of parity in female subjects and LUTS also showed a statistically significant association with P-value of 0.015.

As shown in Table 1, from 94 female subjects (71.76%) with at least one child, 69 subjects had LUTS, as inidicated in Table 3. Approximately half of these subjects had a parity amount of 3 or higher, while the other half had a parity amount below 3 (36 subjects vs. 33 subjects). Female subjects with a parity amount of 3 or higher had a 1.35 times higher chance of developing LUTS compared to those with a parity amount lower than 3. After adjusting for regular amlodipine drug consumption, a very strong positive association was observed between female subjects with a parity amount of 3 or higher and LUTS, as indicated by an aPR value of 9.38 (95% CI 7.38-11.93).

TABLE 3 Characteristics associated with LUTS presence

Characteristics	LUTS Category		PR (95% CI)	aPR[A] (95% CI)	*P*-value
	LUTS Present (IPSS >=1)	LUTS Absent (IPSS 0)			
	n (%)	n (%)			
Age					
Age >=60	38 (92.68)	3 (7.32)	**1.36 (1.15-1.61)**	**3.05 (2.59-3.61)**	**0.002***
Age <60	61 (67.78)	29 (32.22)			
Sex					
Male	30 (81.08)	7 (18.92)	1.1 (0.9-1.34)	2.47 (2.02-3.01)	0.357
Female	69 (73.4)	25 (26.6)			
Overweight					
Yes	29 (82.86)	6 (17.14)	1.13 (0.93-1.37)	2.54 (2.09-3.08)	0.241
No	70 (72.92)	26 (27.08)			
Hypertension					
Yes	78 (91.76)	25 (8.24)	1 (0.79-1.28)	2.25 (1.77-2.87)	0.936
No	21 (45.65)	7 (54.35)			
Hyperglycemia					
Yes	87 (88.78)	11 (11.22)	**2.44 (1.54-3.85)**	**5.46 (3.45-8.62)**	**<0.001***
No	12 (36.36)	21 (63.64)			
Education level					
Elementary school or lower	75 (75.76)	24 (24.24)	1.01 (0.8-1.27)	2.25 (1.79-2.84)	0.930
Higher than elementary school	24 (75)	8 (25)			
Alcohol consumption					
Ever consumed	1 (50)	1 (50)	0.65 (0.16-2.64)	1.47 (0.36-5.9)	0.442[F]
Never consumed	98 (75.97)	31 (24.03)			
Smoking status					
Active smoker	19 (86.36)	3 (13.64)	1.17 (0.96-1.43)	2.63 (2.15-3.21)	0.196
Non-smoker or former smoker	80 (73.39)	29 (26.61)			
Occupation					
Unemployed	46 (76.67)	14 (23.33)	1.02 (0.84-1.24)	2.29 (1.89-2.79)	0.788
Employed	53 (74.65)	18 (25.35)			
Monthly income					
< Rp 2000k	78 (77.23)	23 (22.77)	1.1 (0.85-1.42)	2.46 (1.9-3.19)	0.418
>= Rp 2000k	21 (70)	9 (30)			
Sexual activity					
Regular or at least once in the past month	51 (72.86)	19 (27.14)	0.92 (0.76-1.12)	2.07 (1.7-2.51)	0.438

Never or no sexual activity in the past month	48 (78.69)	13 (21.31)			
DM2 diagnosis duration					
>=5 year	38 (90.48)	4 (9.52)	**1.32 (1.11-1.56)**	**2.95 (2.48-3.5)**	**0.006***
<5 year	61 (68.54)	28 (31.46)			
Regular hypertension drug consumption (1 month)					
Yes	52 (74.29)	18 (25.71)	0.96 (0.79-1.17)	2.15 (1.77-2.61)	0.713
No	47 (77.05)	14 (22.95)			
Regular amlodipine consumption (1 month)					
Yes	52 (91.23)	5 (8.77)	**1.43 (1.18-1.73)**	Av	**<0.001***
No	47 (63.51)	27 (36.49)			
Parity (Female)					
>=3	36 (85.71)	6 (14.29)	**1.35 (1.06-1.71)**	**9.38 (7.38-11.93)**	**0.015***
<3	33 (75.73)	19 (36.54)			

n : Frequencies
PR : Prevalence Ratio
aPR : Adjusted Prevalence Ratio
A : Adjusted for Regular amlodipine drug consumption (1 month)
F : Fisher's Exact Test
Av : Adjustment Variable
* : Significant P-value

Discussion

LUTS encompasses a range of symptoms related to the urinary system and can be divided into storage symptoms, voiding symptoms, and post-voiding symptoms [10]. Several factors have been studied in association with LUTS, and one of the most influential factors is diabetes [6,8,12,14]. Unlike the majority of studies on LUTS that focus on specific populations based on gender, age, or associated diseases that are directly related with LUTS, our study screened all subjects diagnosed with DM2 without any confounding comorbidities. We aimed to reflect the prevalence and elucidate the factors of LUTS in DM2 without being influenced by other specific diseases. Although the LUTS prevalence has shown variation in many studies, the prevalence was expected to be high in the DM2 population as depicted in our study [6,12,14]. The varied prevalence observed in different studies can be attributed to variations in study methods, different definitions of LUTS, or some studies calculating LUTS prevalence based on specific genders or diseases such as BPH.

In our study, the LUTS prevalence in DM2 was 75.57%, with a higher prevalence in male subjects (81.08%) compared to female subjects (73.4%). More than half of the subjects had mild LUTS (62.63%), while one third had moderate LUTS (32.32%), and a small portion had severe LUTS (5.05%). However, a greater proportion of male subjects had severe LUTS (13.33%) compared to female subjects (1.45%). These findings are consistent with a study by Booth et al., which reported that males tend to have higher IPSS scores and more severe LUTS compared to females [22]. Although all subjects had never been diagnosed with any urological diseases, this does not rule out the risk of BPH (Benign Prostatic Hyperplasia) and Bladder Outlet Obstruction (BOO) in male subjects. The risk of BPH is supported by the fact that almost all

male subjects with severe LUTS were aged 60 or older, as age is one of the most influential factors in BPH and contributes to an increase in prostate size [23-26]. In addition, DM2 and hyperglycemia may exacerbate the pathogenic mechanism of BPH through vascular damage complications associated with DM2, which can lead to tissue hypoxia and the induction of growth factors that contribute to prostate enlargement [9]. Given these facts, further urological assessment is necessary to evaluate the presence of BPH in these subjects.

We found a statistically significant association between age and the presence of LUTS in DM2 (p-value 0.002). Subjects aged 60 or older had a 1.36 times higher chance of experiencing LUTS compared to subjects below 60 years old. A study by Qasrawi et al., which investigated LUTS in the DM population, also reported a similar finding [6]. This finding is consistent with other studies that have identified age as one of the most influential factors in LUTS [6,12,14,27]. Like in the general population, the correlation between age and LUTS in DM2 can be attributed to the degenerative processes that occur in the urinary tract functions as advancing age. In line with other study results, gender, education level, occupation, monthly income, and sexual activity showed no association with LUTS [6,14]. However, contrary to findings from other studies, smoking status and alcohol consumption in our study showed no statistically significant association with LUTS in DM2 [12,14]. Theoretically, light alcohol consumption may increase the probability of LUTS by elevating sympathetic nervous activity or inducing diuretic effects on the vasopressin system, while moderate to high alcohol consumption may decrease the probability of LUTS by inducing estrogen receptor or decreasing total dihydrotestosterone levels in the prostate [12]. The effects of smoking are associated with the worsening of storage symptoms or elevation of serum testosterone levels caused by nicotine [12]. We acknowledge that our results regarding the association of smoking status and alcohol consumption with LUTS in DM2 could be questionable due to the small proportion of subjects who were active smokers (16.79%) or had ever consumed alcohol (1.53%). The parity amount of 3 or higher in female subjects was found to be associated with LUTS in DM2, with a P-value of 0.015 and a PR value of 1.35 (95% CI 1.06-1.71). The combination of a parity amount of 3 or higher in female subjects and regular amlodipine consumption in the past month showed a very high elevation in the risk of LUTS in DM2, as shown by an aPR value of 9.38 (95% CI 7.38-11.93). The majority of parities in female subjects were through vaginal delivery. This could be explained by the repetitive injuries to peripheral pelvic nerves and direct trauma to pelvic support tissues [12]. A study by Micussi *et al.* showed that females with insulin resistance such as in DM2 patients have a lower Electromyography (EMG) activity in Pelvic Floor Muscles (PFMs) that may indicate weaker strength of PFMs in DM2 subjects [28]. This fact was also supported by the study of Zhang et al. and also stated in a study by Wang *et al.*, which reported that females who underwent vaginal delivery were more likely to have storage symptoms [12,29].

Overweight, as calculated by BMI, was not found to be statistically significant associated with LUTS in DM2 in our study (P-value 0.241), although there is a positive association between overweight and LUTS, as indicated by the PR value of 1.13 (95% CI 0.93-1.37). Surprisingly, these findings differ from most studies that have reported a higher BMI being associated with LUTS in DM2 [6]. The difference could be explained by the fact that 73.28% of the subjects in our study had a normal or underweight BMI. We acknowledge that this fact may have influenced the true value of the association between overweight and LUTS.

One of the most statistically significant associations observed is hyperglycemia (P-value <0.001). Subjects with hyperglycemia were 2.44 times more likely to have LUTS in

DM2. Even after adjusting for regular amlodipine drug consumption in the past month, this chance doubled to 5.46 times. Although we were unable to categorize subjects as having uncontrolled DM2 due to the limitation of not having HbA1c examination, the strong association between hyperglycemia and LUTS suggests that high blood glucose levels increase the likelihood of LUTS. It is well known that one of the earliest symptoms of DM2 is increased frequency (polyuria) [7]. This can be explained by the fact that the kidney's capacity to absorb blood glucose is exceeded, leading to the wastage of excess glucose in urine and an increase in frequency [30-32]. This may be attributed to glucose-induced osmotic diuresis, where excess blood glucose causes an increase in urine excretion [33]. Consistent with hyperglycemia, the duration of DM2 diagnosis also showed a statistically significant association with LUTS in DM2 (P-value 0.006). Subjects who were diagnosed DM2 in 5 years or more had a positive association with LUTS in DM2, as indicated by a PR value of 1.32 (95% CI 1.11-1.56). This correlation could be attributed to the development of complications associated with DM2 over multiple years, such as diabetic neuropathy and diabetic nephropathy [5]. These complications may develop to urological complications, with diabetic bladder dysfunction (DBD)/diabetic cystopathy being the most common, which manifesting as storage symptoms like overactive bladder (OAB), urge incontinence, and voiding symptoms like poor emptying [34]. Therefore, further evaluation is needed to determine the etiology of LUTS in these subjects.

Unexpectedly, there is no association between hypertension and LUTS in DM2, as indicated by a P-value of 0.936 and a PR value of 1 (95% CI 0.79-1.28). This finding contradicts most studies that suggest a significant association between hypertension and LUTS [12,35,36]. In our study, subjects with hypertension were defined based on blood pressure examinations conducted during this study. However, these subjects were different from those who regularly consumed hypertension drugs (Captopril and/or amlodipine) in the past month as they had already been diagnosed with hypertension prior to this study, regardless of their blood pressure levels during examination in this study. Regular hypertension drug consumption in the past month and LUTS in DM2 showed no statistically significant association with P-value of 0.713, moreover, the result of PR value of 0.96 (95% CI 0.79-1.17) indicating a negative association. However, when specifically analyzing the effects of amlodipine, the result obtained a statistically significant P-value of <0.001. Amlodipine, a calcium channel blocker (CCB), is known to cause nocturia [37]. This fact was supported by our research, which showed a positive correlation between regular amlodipine consumption in the past month and LUTS in DM2, with a PR value of 1.43 (95% CI 1.18-1.73). Adjusting for this factor resulted in an increased risk for all factors, as reflected by a doubling or greater elevation in the aPR value.

Regardless of the types and etiologies of LUTS, it is a common symptom in DM2 patients and can be caused by diabetic complications. Early diagnosis and evaluation are crucial in order to prevent further worsening of symptoms and slow down the progression of diabetic complications. PHC and GPs, being the most accessible healthcare facilities, should be capable of screening and assessing the severity of LUTS. Early medication and conservative management should be initiated at the PHC level, while also identifying the underlying pathologies to determine the criteria for patient referral. It is widely recognized that the first and easiest intervention for LUTS in DM2 patients is lifestyle modification, including regular exercise, weight loss, and, most importantly, tight control of DM2 [6]. We recommend ensuring the availability of other diabetic and hypertension drugs at PHC centers, considering the high proportion of

uncontrolled DM2 cases and the potential side effects of amlodipine. We also recommend a regular screening of LUTS in DM2 patients. National standardized evidence-based guidelines are necessary to assist GPs in PHC centers in determining appropriate management strategies.

To the best of our knowledge, this was the first study conducted in Indonesia that examined the prevalence of LUTS specifically in the DM2 population and explored the associated factors. The study included subjects of both genders and examined multiple factors in all subjects. Furthermore, we used a validated Indonesian version of the IPSS questionnaire, which added strength to our study. However, it is important to consider that our study was conducted in PHC, which may not fully represent the wider population. The unavailability of certain examination tools limited our ability to obtain more objective data, and the cross-sectional design of our study prevented us from establishing causal relationships for the significant associations found in our results.

Conclusion

The majority of DM2 patients experience unreported LUTS, reflecting a significant burden in DM2 patients. Factors such as age, hyperglycemia, duration of DM2 diagnosis, regular consumption of amlodipine in the past month, and parity in female subjects were found to be associated with LUTS in DM2. Prolonged uncontrolled DM2 could accelerate the progression of diabetic complications, worsening the underlying pathologies contributing to LUTS. Proper management and tight control of DM2 are crucial, and regular screening for LUTS should be conducted in all DM2 patients.

Acknowledgments

We thank Dr. Teguh Triyono (University of Gadjah Mada) for providing advice and helping any administration process for this study.

Funding

This study was self-funded by the authors, and no external sources of financial support were involved. The authors personally covered all expenses related to study design, data collection, analysis, interpretation, and manuscript preparation.

Authors' Contributions

NY as the first author made a conception, data collection, and data calculation. MRUA and MIFA made a substantial contribution to the literature review and data interpretation.

Ethical Approval

This study has been approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University, Indonesia (310/UN1/FK-KMK.3/PK.2/TL/2023).

Conflict of Interest

The authors have no conflict of interest in the subject matter or materials discussed in this manuscript.

Orcid:

Noka Yogahutama:*
https://orcid.org/0009-0004-2012-0533
Muhammad Rifqi Ulil Abshor:
https://orcid.org/0009-0007-2558-9252
Muhammad Isa Fuad Affan:
https://orcid.org/0009-0009-2594-4992

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How to cite this article: Noka Yogahutama, Muhammad Rifqi Ulil Abshor, Muhammad Isa Fuad Affan, Analysis of lower urinary tract symptoms (LUTS) in diabetes mellitus type 2 (DM2) patients at an indonesian primary health care: A cross-sectional study. *Journal of Medicinal and Pharmaceutical Chemistry Research*, 2024, 6(9), 1312-1326. **Link:** https://jmpcr.samipubco.com/article_193842.html