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Role of calcium channel blockers in lower urinary tract symptoms in benign prostatic hyperplasia: a literature review

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Abstract

Background: Benign prostatic hyperplasia (BPH) and the use of CCBs are common in older persons, and are also associated with lower urinary tract symptoms (LUTS). This review summarised and synthesised relevant information and recent advances to improve clinical knowledge on the role of CCBs in LUTS, BPH symptoms and health-related quality of life.

Main body of the abstract: A search of databases of PubMed, Web of science, Hinari, and Google scholar was performed using several keywords. Relevant studies were also extracted from references of identified studies. Selected studies were assessed for content related to CCBs, BPH and LUTS, and the most relevant reports were included. The inhibition of calcium channels by CCBs interferes with influx of extracellular Ca^{2+} into the detrusor muscle, which interferes with bladder contraction and relaxation. Hence, CCBs are associated with precipitation or aggravation of urinary storage and voiding symptoms, which are also common symptoms of BPH. This suggests a potential aggravation of BPH symptoms with the use of CCBs.

Short conclusion: Persons at high risk of LUTS such as in BPH, may benefit from other classes of antihypertensive drugs. Therefore, it is essential to identify persons with BPH prior to commencement of therapy with CCBs. Patients on CCBs should be routinely reviewed for any potential precipitation or aggravation of LUTS. Patients should also be counselled to notify their healthcare provider of unusual urinary symptoms during CCB use. This will facilitate enhanced quality of life in patients with BPH.

Keywords: Calcium channel blockers, Benign prostatic hyperplasia, Lower urinary tract symptoms, Amlodipine

1 Background

Calcium channel blockers (CCBs) are commonly used antihypertensive medicines [1], and are associated with the development of lower urinary tract symptoms (LUTS) [2–5]. This occurs as a result of its interference with bladder contraction [6–8]. Arising from the blockade of L-type calcium channels in detrusor muscles, CCBs are associated with increased duration for bladder maximum contraction, maximal rate of emptying and rate of filling. These may result in LUTS such as voiding and storage symptoms [9], including overflow incontinence [10]. Amlodipine appears to be more frequently associated with LUTS [11], particularly pollakiuria and other obstructive symptoms. Severe LUTS is also significantly associated with amlodipine, nifedipine, diltiazem and verapamil [3], while highly vascular selective CCBs such as felodipine and lercanidipine are associated with less risk of LUTS [3]. However, LUTS secondary to CCBs are likely to resolve after discontinuation of the CCB [3, 5]. In contrast, an animal study found amlodipine to be associated with improved LUTS in BPH rats [12]. LUTS is common among men over 40 years of age, and its

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prevalence increases with age [10, 13–15]. Meanwhile, other conditions such as benign prostatic hyperplasia (BPH) also present with LUTS [16].

BPH and hypertension are common conditions in ageing men [17]. BPH is a chronic age-related enlargement of the prostate gland [17] and occurs at varying prevalence among different populations. Although a prevalence of 13.84% to 23.79% was reported for the Middle East countries [18], a global prevalence of 20.0% – 62.0% has been reported among men over 50 years [19]. It is mostly associated with family history, lifestyle, other chronic diseases (diabetes and hypertension) and medications [3, 17]. Following age-related increase in prostate, there is increased risk of LUTS from prostatic obstruction and decrease in urethral sphincter function in older men [20, 21]. This is associated with LUTS such as weak urinary flow or interrupted urine streams, difficulty initiating urination, urinary retention, increased urinary frequency, nocturia, and incomplete bladder emptying, among others [22]. A high prevalence (72.0%) of moderate LUTS among BPH patients was observed in a previous study [23]. LUTS is a significant cause of morbidity, manifesting as irritative or obstructive symptoms and worsens with age.

Available evidence is suggestive of association of CCBs and BPH with LUTS [2–5, 17]. Following recent guideline from the World Health Organisation, CCBs are among the first line medications for the management of high blood pressure [24]. However, there appears to be poor attention and recognition of its associated LUTS in clinical practice. These LUTS effects may result in exacerbation of urological symptoms of BPH. Meanwhile, there is paucity of evidence on the relationship between CCB-related LUTS and its associated impact in BPH, including patients' quality of life. Although few, previous studies have focused only on associations of antihypertensives with LUTS. This review was aimed at summarising and synthesising basic information and recent advances to improve clinical knowledge of the role of CCBs in LUTS and its implication in BPH, including associated impact on patients' quality of life.

2 Main text

2.1 Study design

A non-systematic review of relevant articles retrieved from electronic databases of PubMed, Web of science, Hinari and Google scholar was performed.

2.2 Search strategy

Keywords used for the search include: calcium channel blockers, lower urinary tract symptoms, benign prostatic hyperplasia, nocturia, urinary retention, calcium channel antagonists, urinary symptoms and quality of life. Keywords were searched in appropriate combinations, they were also used in series and through truncation. Relevant studies were also extracted from references of identified studies.

2.3 Selection criteria

2.3.1 Eligibility criteria

Published articles on LUTS-related effects of CCBs, its implications for BPH and associated quality of life, from year 1991 to 2022 were considered eligible for this review. Abstracts of relevant articles were screened for eligibility. Articles that reported the role of calcium channel blockers in LUTS, impact of calcium channel blockers-related LUTS on urological symptoms of BPH, and impact of calcium channel blockers-related LUTS on quality of life of BPH patients, were considered eligible for the review.

2.3.2 Inclusion and exclusion criteria

Relevant case studies and original articles on preclinical and clinical studies that reported association of CCBs and LUTS, its implications on BPH and patients' quality of life, published in English were included in the study. However, commentaries, opinions, editorials and correspondences were excluded.

2.4 Data extraction

Selected studies were assessed for content related to CCBs, BPH and LUTS, and the most pertinent reports were extracted and incorporated into this review.

2.5 Outcome measures

Outcomes of interest were:

Role of calcium channel blockers in LUTS.

Impact of calcium channel blockers-related LUTS on urological symptoms of BPH.

Impact of calcium channel blockers-related LUTS on quality of life of BPH patients.

2.6 Case definition

LUTS refers to all symptoms of bladder storage dysfunction (which includes, nocturia, increased frequency of daytime urination, urinary urgency and incontinence), voiding dysfunction (such as, weak stream, splitting and spraying, hesitancy, intermittency, straining and terminal dribble) and post-micturition (such as, sensation of incomplete bladder emptying and dribbling after micturition) [25].

2.7 Associated pathway for BPH and hypertension

Same pathophysiology pathway relating to sympathetic nerve activity has been linked with concomitant BPH and hypertension. They are both associated with age-related upregulation of sympathetic nerve activity [26]. The associated increase in blood pressure following increase in

heart rate and total peripheral resistance is commonly and widely managed with CCBs [1]. Contraction of the prostatic smooth muscle is another outcome of increased sympathetic nerve activity. Bladder outflow obstruction mediated by BPH as a result of the autonomic nervous system, is a predisposing condition for LUTS [26].

2.8 Pathogenesis of BPH and LUTS

Androgenic hormones are important contributors to the development of BPH. Testosterone and dihydrotestosterone are involved in the hyperplastic process that produces the growth of glandular epithelial and stomal tissues in the prostate [27]. This process results in increase in the prostate gland, arising from loss of homeostasis between cell proliferation and cell death [28]. The pathologic process gives rise to additional cells in the periurethral area which causes enlargement of the prostate and squeezes the urethra, thereby limiting urine outflow [28]. BPH results in a varying degree of benign prostatic obstructions (BPO). This usually presents as LUTS (obstructive uropathy), and may result in bladder or kidney-related complications. This distinguishes BPH from other causes of LUTS.

LUTS occurs as a result of complex interaction between the bladder and urinary outflow tract. Therefore, factors that affect the bladder function, the prostate and urethra are important in the aetiology of LUTS [29]. Aside obstructive uropathy and drug-related uropathy, urothelium dysfunction is also implicated in LUTS. The urothelium bladder barrier and afferent receptor lining produces stimuli in response to local changes. It is also associated with paracrine and autocrine secretory functions which impacts on the adjacent urothelium, nerves and blood vessels [30]. Therefore, dysfunctions that interfere with these pathways are associated with disruption of normal signalling pathways and subsequent development of LUTS [31]. Drug-related aetiology of LUTS is also recognised, and several drugs are implicated, including CCBs.

2.9 Effects of CCBs on detrusor muscles of the bladder

Calcium channels are essential for normal bladder function [8], and detrusor muscles are the bladder smooth muscles responsible for bladder contraction and relaxation. Preclinical and clinical studies have shown the critical role of calcium influx through L-type calcium channels in bladder contraction [32–34].

Influx of Ca^{2+} into intracellular store of the detrusor muscles through voltage-dependent dihydropyridine-sensitive Ca^{2+} channels is essential for normal bladder contraction [32]. This was demonstrated by Rivera et al. in a study of mammalian urinary bladder [32]. The study was conducted with the urinary bladder of a guinea pig, and demonstrated the effects of a dihydropyridine CCB (nifedipine) on the bladder under polarised and depolarised conditions. Findings from the study showed that nifedipine largely inhibited carbachol-induced bladder contractions under polarised conditions, and inhibited priming and store-release contractions under depolarised condition. Although this study was not conducted on human bladder, it shows that L-type Ca^{2+} inhibitors are potent inhibitors of bladder contraction and affect the normal contraction ability of detrusor muscles which interferes with the ability to achieve normal voiding [33]. Meanwhile, the amount of intracellular free Ca^{2+} regulate the tone of the detrusor smooth muscles [8, 33].

In a human study, Masters et al. assessed the effect of Ca^{2+} release on induced bladder contraction [33]. The study found that diltiazem (CCB) reduced contraction of the bladder smooth muscles. This suggests that L-type CCBs significantly interfere with the intracellular store release of Ca^{2+} influx required to activate the contraction of detrusor muscles.

Similarly, a previous in-vitro study showed a high suppression of spontaneous urethral activity by CCBs [15]. The CCBs were also noted to partially block electrically as well as agonist-induced detrusor contractions [15]. Furthermore, some CCBs have also been associated with anticholinergic properties and may cause anticholinergic symptoms which include urinary retention.

2.10 LUTS associated with CCBs and BPH

There are overlapping LUTS symptoms between impaired detrusor activity (in CCB use) and bladder outlet obstruction (BOO) such as BPH [35]. Detrusor underactivity (which is associated with CCBs) is more frequently associated with several LUTS which include, decreased bladder sensation, urine hesitancy, incomplete bladder emptying and decreased/interrupted urine flow. However, Rademakers et al. demonstrated the differentiation of LUTS associated with detrusor muscle underactivity and BOO [36]. Their study showed that impaired detrusor muscle activity and bladder outlet obstruction are differentiated by pressure-flow studies with adjusted threshold values for the impaired bladder activity for BOO-grade [36]. The researchers noted that a nomogram using BOO-index and maximum Watts factor is a highly relevant tool for identifying detrusor underactivity and/or BOO. Values below the 25^{th} percentile line indicate detrusor underactivity [36].

Oelke et al. also noted that a nomogram enables the differentiation of impaired detrusor contractility and BOO in men with LUTS [37]. The retrospective study comprised men who had LUTS, and were ≥ 40 years old. It found that a measurement of detrusor underactivity $< 25^{th}$

percentile correlates with clinical indicators of detrusor underactivity (which is also associated with the use of CCBs), and is suggested as a cut-off value for detrusor underactivity diagnosis. Although with a risk of observation bias inherent with retrospective studies, the study reported specific indications of detrusor underactivity to include higher age, bladder capacity, lower voiding efficiency [37] and use of CCBs [33].

2.11 Role of CCBs in urinary retention and effect in BPH

Detrusor muscle is the main muscle component of the urinary bladder wall, and its contraction and relaxation ability determine the bladder function during filling and micturition. Blockade of extracellular Ca^{2+} resulted in the blockade of carbacol (CCh)-induced contraction in a previous animal study [8]. Free Ca^{2+} is critical for activation of the contraction of detrusor muscle [33], therefore, the inhibition of this free Ca^{2+} by CCBs is associated with urinary retention or increased severity of urinary retention, intermittent stream, urinary hesitancy, straining, poor stream, terminal dribbling and incomplete bladder emptying in BPH. However, assessed studies focused on other presentations of LUTS.

2.12 Role of CCBs in urine storage dysfunction (nocturia) and BPH

Nocturia is defined as the need to void urine during sleeping period at night, while ≥ 2 is clinically relevant nocturia [38]. It is usually caused by increase in urine volume at night or decrease in bladder capacity. Nocturia is associated with age and BPH, however its occurrence has also been associated with the use of some CCBs, from which it may be aggravated in pre-existing states [39]. The association of CCBs with nocturia has been reported in several studies [2, 40]. Unlike other antihypertensive medications, clinically important nocturia is independently associated with the use of a CCB [40].

In their study, Washino et al. noted that patients who took CCBs had more episodes of nocturia than the others [40]. The researchers evaluated nocturia using item 7 of the international prostate symptom score (IPSS) questionnaire, in their retrospective evaluation of men who were ≥ 40 years of age. The study found CCBs to be independently associated with clinically important nocturia. Although with an inherent risk of observation bias of retrospective studies, findings suggest significant association between nocturia and the use of CCBs. New onset and aggravation of previously existing nocturia during use of CCBs was also reported by Hall et al. [2]. In the population-based study, CCB monotherapy was noted to be associated with elevated prevalence of nocturia. The study comprised a large sample size, and interviewer administered questionnaire was used for data collection.

Higher incidence of nocturia is associated with CCBs than in aldosterone receptor antagonists, β-blockers, ACEIs and ARBs [3]. Age is also another notable factor associated with nocturia [40]. Mankowski et al. noted that men with LUTS/benign prostatic hyperplasia preferred treatment that relived both urgency and day time/night time micturition as a compensation for potential side effects [41]. Patients with BPH and LUTS have more bladder storage dysfunction, whereas patients with BPH and severe LUTS have higher grade of bladder outlet disorders associated symptoms [42]. Detrusor underactivity or BOO or both are also associated with storage dysfunctions [43].

2.13 Role of CCBs in voiding dysfunction (urinary frequency and urgency)

CCBs are particularly associated with voiding-related symptoms of LUTS [2]. This was reported by Hall et al. in their 3-year study of urological symptoms in adults who used CCBs and other antihypertensive medications [2]. The large sample sized, population-based, cross-sectional study assessed urological symptoms by the American Urological Association Symptom index. Findings from the study suggests a review of CCBs use in worsening or new onset of voiding disorders. This is particularly relevant for patients with pre-existing voiding disorders as seen in BPH.

Association of voiding disorders and the use of CCBs was also reported by Elhebir et al. [3]. This was assessed in a cross-sectional study by the IPSS questionnaire, among in-patients of ≥ 40 years old who used CCBs. The study noted that Amlodipine/nifedipine and diltiazem/verapamil had very significant association with severe LUTS and moderate-to-severe LUTS in all study participants.

Although with a small sample size, another study reported a significant association between LUTS and use of CCBs in men ≥ 45 years old [44]. Findings from the study showed worsened LUTS in urinary obstructions when CCBs were initiated. A previous case report also associated amlodipine (a dihydropiridine CCB) with LUTS, particularly, urinary frequency, nocturia and occasional incomplete bladder emptying [5]. Incomplete emptying of the bladder is another frequently reported LUTS and is significantly associated with worsening of storage and voiding symptoms [45]. Voiding dysfunction can result from detrusor underactivity following alteration of Ca^{2+} influx, or BOO such as BPH, or both [43]. Meanwhile, detrusor overactivity was reported to be an independent factor for BOO [43].

2.14 Role of CCBs in post-micturition symptoms and in BPH

Post-micturition symptoms are common in persons with BPH and they include sensation of incomplete bladder emptying and dribbling. It involves the involuntary loss of urine immediately after urination [44]. Previous studies have associated the use of CCBs with post-micturiction symptoms [5, 45]. However, it mostly results from weakness or failure of the pelvic floor muscle [44], or from inability of the bulbocavernosus muscle to perform a normal reflex post-void milking mechanism or urethrocavernosus reflex [46]. Post-micturition symptoms is prevalent among persons with BPH and increases with age, but symptoms may be less severe [47]. It occurs when urine in the bulbar urethra slowly leaks out after urination [48]. It is associated with urinary obstructions such as BPH [48] or detrusor underactivity [5, 45]. Although nifedipine is associated with significant increase in residual urine, there is paucity of evidence for association of post micturition symptoms with CCBs.

2.15 Impact of CCB-related LUTS on quality of life including in BPH

There is paucity of data on impact of CCB-related LUTS on the quality of life of persons with BPH. However, the use of CCBs in BPH is associated with worsening of LUTS, and a significant reduction in quality of life [44]. This assessment by Hughes et al. was performed using the International Prostate Symptoms Score Quality of Life (IPSS-QoL) index which ranges from 0 (delighted) to 6 (terrible) [44]. Although not peer reviewed, Elhebir et al. also demonstrated higher LUTS-related quality of life in non-CCB users than in CCB users [11]. LUTS appear to have varying effects on QoL dimensions. Storage symptoms tend to decrease QoL more than voiding and post micturition symptoms as noted by Engstrom et al. [49]. In their study, storage symptoms such as nocturia and moderate to severe degree of weak stream were associated with lower QoL than voiding symptoms and post-micturition symptoms [49]. Although this study was not specific for only CCB users, it provides insight on potential lower QoL of life in persons with storage symptoms of LUTS, which is mostly seen in CCB-related LUTS.

Although poor health status and QoL is associated with adult men of all ages with mild to severe LUTS [13, 15], older age is also associated with lower LUTS-related QoL [15]. This is observed from the IPSS QoL which showed a higher prevalence of lower LUTS-related QoL in older men [49]. A previous study noted that QoL also decreases with increase in severity of LUTS, as moderate to severe LUTS significantly impact on general health-related QoL [50]. The observational study had a large sample size, but included only BPH patients, without focus on CCB use. Medical treatment of BPH or withdrawal of CCBs in LUTS secondary to BPH or CCBs results in improved QoL [51].

LUTS consistent with BPH and CCBs use, can be bothersome and negatively impact on patient's QoL [52]. LUTS/BPH is associated with higher direct medical costs and indirect losses in daily functioning, which negatively impacts on patients and partners [52]. It is also associated with psychological and economic impact requiring close attention to prevent further reduction in QoL. It is a significant health problem with considerable social and economic impact [53]. Men with LUTS are at significantly higher risk of falls which are associated with fractures, pains and debilitating morbidities [22, 54].

2.16 Implication of CCBs-induced LUTS in BPH

BPH is the most common aetiology of LUTS in men. It is independently associated with the onset and progression of LUTS. LUTS constitutes serious morbidities, lower QoL and negative impacts on productivity. Aggravation of these symptoms and associated impacts are potentially associated with the use of CCBs in BPH patients, following potential additive effects. This presents as increased storage and voiding symptoms [2, 3, 40, 44]. Using the IPPS questionnaire, Hughes et al. found that CCBs worsened LUTS in males with urinary obstructive conditions such as BPH, and was also associated with reduced QoL [44]. Therefore, careful assessment and substitution of CCBs are critical for improved symptoms in LUTS secondary to CCBs in BPH patients.

2.17 Clinical significance

Appropriate patient monitoring, adequate medication counselling and proper drug information are critical for maximum benefits from CCBs. Drug information should be available to the patients and prescribers [55, 56] for quick identification and management of adverse drug reactions relating to LUTS, particularly in persons with BPH. This management should include complete withdrawal of a CCB and its replacement with a more appropriate medication for the individual patient.

Among clinicians, knowledge of the role of CCBs in detrusor underactivity will aid in reducing the burden of LUTS in BPH patients, as this awareness will influence patients' drug therapies. This is particularly important during the development of patient's management plan, to reduce the risk of LUTS aggravation in persons with BPH [57]. In clinical practice, CCB induced LUTS may warrant unnecessary medication therapy, which could be prevented by increased awareness of CCBs associated LUTS. More so, a careful medication history enables the prescriber's understanding of patients' experiences with

drug treatments, particularly, medication-induced conditions such as LUTS [57]. Therefore, it is necessary to evaluate antihypertensive medicines of patients presenting with LUTS, prior to initiation of therapy by urologists.

2.18 Role of pharmacists

The pharmacists' role involves provision of up-to date and clinically relevant drug information to prevent aggravation of LUTS, slow the clinical progression of BPH symptoms and improve patients' QoL [58]. The current patient-centred care of pharmacy practice has enhanced in-depth medication-related communication [59, 60] for increased benefits. This communication is achieved during medicine dispensing [59, 60], monitoring or routine drug information services [55]. Among the several roles of clinical pharmacists are assessment of patients' medical and medication history, identification of patients at risk, and prevention of LUTS, in collaboration with the patients and physicians. Provision of routine and consistent drug therapy monitoring in patients on CCBs and BPH patients is a critical role of pharmacists that potentially enables early identification of onset or aggravation of LUTS [61]. Enhanced medication outcome is also achieved by providing patient education on potential adverse effects of CCBs, with proper information on steps to take if LUTS is noticed or aggravated [62].

2.19 Study limitations

Although available data show the role of CCBs in LUTS and its implication for BPH, only few studies were available for the years in review. Also, the search in only four database may have excluded potentially relevant articles. The complete reliance on previously published articles may also pose some limitations to this review, as availability of eligible articles and quality of articles are put into consideration.

3 Conclusions

Persons at high risks of LUTS such as BPH patients, may benefit from other classes of antihypertensive drugs. Therefore, efforts at identifying high-risk LUTS persons prior to commencement of therapy with CCBs are essential. Patients on CCBs should also be routinely reviewed for any potential precipitation or aggravation of LUTS. Patients should also be counselled to notify their healthcare provider of unusual urinary symptoms during CCB use. This will facilitate enhanced quality of life of high-risk patients, such as those with BPH.

Abbreviations

CCBs: Calcium channel blockers; LUTS: Lower urinary tract symptoms; IPSS: International prostate symptom score; BPH: Benign prostatic hyperplasia; QoL: Quality of life; BOO: Bladder outlet obstruction.

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Author contributions

COI conceived and designed the study with substantial contribution from CNO and AKE. COI conducted the literature search and wrote the initial draft with substantial contributions from CNO and AKE. All authors revised and approved the manuscript.

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Competing interests

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