Chapter 17
Treatment of Hypertension in Light of the New Guidelines: Drug Adherence

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Introduction

Hypertension is frequently observed in patients with chronic kidney disease (CKD) [1] with an increasing prevalence as the glomerular filtration rate falls. Hypertension is an important issue in the care of CKD patients as it is an important determinant of the progression to end-stage renal disease and to protect against cardiovascular disease [2]. Therefore, an adequate control of blood pressure in these patients results in a slower decline in renal function [3] and is recommended in all patients with CKD. However, to achieve these goals, adherence to treatment plays a major role.

When we examine the blood pressure control rates in CKD patients, the story is different. It was shown that the BP control rate remains low in CKD patients with 13.2% of patients having <130/80 mmHg Kidney Early Evaluation Program (KEEP) [4]. Moreover, blood pressure targets were achieved only in 35% of CKD patients in a more recent work [5]. Furthermore, in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, while 36.2% of CKD patients had a BP of >140/90 mmHg, 61.6% of patients had a BP of >130/80 mmHg [6].

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The Term "Adherence" in Patients with Chronic Kidney Disease: The Facts

When the patient reaches to end-stage renal disease, clinical comorbidities like renal anemia, secondary hyperparathyroidism, and infection are much morely added to hypertension that all are involved in the clinical course and survival of the CKD patient. Therefore, progression of CKD is generally associated with introduction of new drugs to be taken by the patient to minimize the effects of these disorders that might be difficult to be controlled only by dietary measures and dialysis therapy itself. Pre-dialysis patients have been shown to be treated with a mean of 6–12 medications [2, 7]. Moreover, a recent study on maintenance dialysis therapy revealed a median number of 19 pills with one-quarter of them taking >25 medications daily [2, 8]. In the light of these findings, the term "drug adherence" defined as patient's respect to taking his/her prescribed medication(s) is a significant issue in this patient population. Additionally, adherence in hypertension emphasizes the need for agreement between the physician and patient in the treatment of hypertension and consequently focuses on the patient's ability and willingness to accept an antihypertensive regimen. Moreover, the World Health Organization (WHO) says that, "adherence is a person's behavior concerning taking medication, following a diet, and making changes in lifestyle in accordance with a medical or non-medical health professional recommendations" [9].

Studies in Chronic Kidney Disease Population

Adherence might be lower in these patients due to such a high pill burden in patients with CKD. Supporting this idea, a low adherence to drug treatments (down to 3%) as well as a low adherence to nutritional recommendations has been reported in CKD and dialysis patients [2, 10]. Moreover, adherence to drug therapy in CKD was assessed via the medication possession ratio [5] and the Morisky questionnaire [6]. The findings of these abovementioned studies revealed that more than 30% of the study patients which is a quite significant number were poorly adherent to medical therapy. Interestingly, a study measuring drug adherence in CKD patients reported improving drug adherence (by self-report) while renal function further declines – indicating both doctors and patients have become more interested in blood pressure control with the progression of CKD [11]. A pre-dialysis study showed that medication nonadherence was lower (17.4%) at the baseline period of the study than after 1 year of the study (26.8%) [11]. Compared to the baseline period, the percentage of adherent patients who became nonadherent (22%) was lower than the percentage of nonadherent patients who became adherent (50%) [11]. Similar numbers were demostrated in CKD patients not on dialysis by Moreira et al. (18.5%) [12] – using the self-report method and a drug profile – and by Lee et al. (18%) [13], based on two methods, pill count and electronic monitoring. It is

also a common finding that in several studies in pre-dialysis, CKD patients reveal that [11, 14, 15] the number of nonadherent patients increases throughout the observation period. This study also showed that nonadherent CKD patients had a higher mean age, were using a larger amount of pills per day at baseline and at the final period, did not self-administer medications, and had higher mean serum creatinine, lower GFR, and a lower frequency of coronary heart disease [11]. In this study, the logistic regression model, adjusted for statistically significant variables in univariate analysis, showed that intake of five or more tablets per day, as well as drug administration by caregivers, was significantly associated with patient's nonadherence [11]. However, problems in adherence to antihypertensive therapy are common in end-stage renal disease patients on dialysis. An Italian hemodialysis study reported that 53% of patients were inadherent to their prescribed drugs, and younger age, male gender, poor social support, increased comorbidities, health beliefs, and depression were the main factors associated with poor adherence [16]. Another European study identified factors associated with nonadherence in hemodialysis patients [10]. Associated parameters were as follows: demographic factors (age, gender, educational level, marital status/living arrangements, race/ethnicity, income/employment status, cost/payment/insurance/socioeconomic situation, smoking/drinking/drug abuse, religion/religiosity), clinical factors (length of time on hemodialysis, chronicity/chronic conditions, diabetic status, former transplant history, treatment regimen complexity/high tablet burden, tablet size and taste, treatment side effects), and psychosocial factors (health beliefs/knowledge/motivation, self-esteem cognitive behaviour/function, health locus of control, social support and family dynamics, psychiatric illness like anxiety/depression) [10].

How can we detect adherence in our patients in a reliable way? Well, the methods – including the widely used Morisky questionnaire, used to measure drug adherence – have disadvantages. They were generally inconsistent and are not very reliable [2]. Moreover, antihypertensive pill counts, questionnaires, patient diaries, and measurement of plasma drug concentrations have been shown to overestimate treatment adherence. Also, there is absence of a common taxonomy in this area. More interesting is that, when different methods are used in the same study, large variations in adherence are observed [2]. Therefore, the lack of effective methods to diagnose adherence problems yields to ineffective improvement in adherence problems. Methods that can be named to near ideal have been mentioned recently [2] as follows: retrospective analysis of prescription refill records [17], analysis of chemical markers of drug exposure [18], and automatic electronic time stamping and compilation of events more or less strongly linked to the act of taking medication (e.g., package opening, dosage form dissolution) [19].

It should always be kept in mind that patients with CKD are so-called a complex medical population that might exhibit significant medication-related problems and medication safety issues during their clinical follow-up [20]. These problems are classified as adverse drug reactions, drug interactions, inappropriate doses, and suboptimal laboratory monitoring [21, 22]. Several studies have examined the rates of adherence to prescribed drugs in patients with CKD involving maintenance renal replacement therapies. The common result of these studies was the frequent finding

of poor adherence among these patients [2]. For example, in recent years, two large studies on hypertension management in CKD population showed that approximately 30% of patients were defined to have a poor antihypertensive drug adherence resulting in uncontrolled blood pressure [5, 6]. Reduced adherence does not only lead to uncontrolled blood pressure but also to poor CKD outcomes [8, 23–25] and to increased mortality in hemodialysis patients as well [26].

Causes of Problems in Drug Adherence in CKD Patients

Potential reasons for nonadherence to pharmacological therapy in both CKD and non-CKD populations can be grouped under three main titles:

Patient-Related Reasons

There are several patient-related reasons for nonadherence to antihypertensive medications. These are as follows:

(a) Forgetting to take medication perhaps because of a busy work or social life [27],
(b) A negative behaviour toward medication
(c) Cultural beliefs
(d) Lack of education
(e) Preconceived beliefs regarding medication
(f) Poor language proficiency

Moreover, patients can make a conscious decision, that is, deciding for themselves the dose and frequency of their antihypertensive regimen.

Physician-Related Reasons

Main thing in this heading is the poor communication between physician and patient as a significant problem that may influence the adherence of patients [28, 29]. The lack of information given by the physician regarding the reason of the initiation of therapy, the impact of hypertension on cardiovascular risk, and the clinical consequences of discontinuation of therapy is of critical importance.

Medication-Related Reasons

Treatment characteristics like complicated regimens (i.e., multiple daily doses of medications), long duration of medical therapy, medications with high cost, and adverse side effect of prescribed therapies (i.e., impotence and effects on mood and sedation) might lead to lower adherence to antihypertensive therapy.

Solutions to Improve Adherence

There are various strategies that can be employed to improve adherence to medication in CKD patients with hypertension:

1. To identify reasons like concerns about polypharmacy, drug interactions, pill size and frequency, cost of drugs, and doubts on the real efficacy of some of the prescribed drugs [30]
2. To educate and maintain significant contact with the CKD patient and the family [31]:
   (a) Information about medications, when written in simple language, is useful [32].
   (b) To avoid broken appointments to clinics by mail, telephone, and clinician reminders [33].
3. To focus on both the patient's and physician's motivations on the necessity of taking antihypertensive therapy [2]
4. To work on simplifying antihypertensive regimens, i.e., the use of fixed-dose combinations or drugs with longer duration of action to prevent the effect of missed doses [2, 34]
5. To work on a team-based strategy involving nephrologists, specialized nurses, and/or community pharmacists in order to enhance the control rates of the various risk factors [35, 36]

Conclusions

Adherence to antihypertensive therapy is a critical component to reduce complications associated with elevated BP in CKD. We should keep in mind that nonadherence is a very common observation in CKD. All the physicians need to understand the importance of improving adherence in their patients and should use or develop the tools to be able to measure it effectively in order to make decisions regarding medication intensification. This would be necessary to achieve optimal clinical outcomes for their patients in the future.

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