



# How to evaluate phosphate control in patients on dialysis

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## IMPORTANCE OF PHOSPHATE REGULATION IN CHRONIC KIDNEY DISEASE

Hyperphosphatemia is associated with negative consequences (e.g. vascular calcification [1]), and is an independent risk factor for cardiovascular (CV) disease [2], the primary cause of mortality in patients with chronic kidney disease (CKD) [2]. Phosphate control to more normal levels of 4.5 mg/dL correlates with improved survival [3]. Both the magnitude of phosphate elevation above the target range (2.5–4.5 mg/dL) and time spent with above-target phosphate levels corresponds to increased CV morbidity/mortality [3]. Thus, reduction and maintenance of serum phosphate toward more normal levels is an established clinical practice guideline: KDOQI guidelines recommend a target of 3.5–5.5 mg/dL in patients with CKD Stage 5 on dialysis [4], and KDIGO guidelines recommend targeting phosphate ‘towards normal’ levels [5].

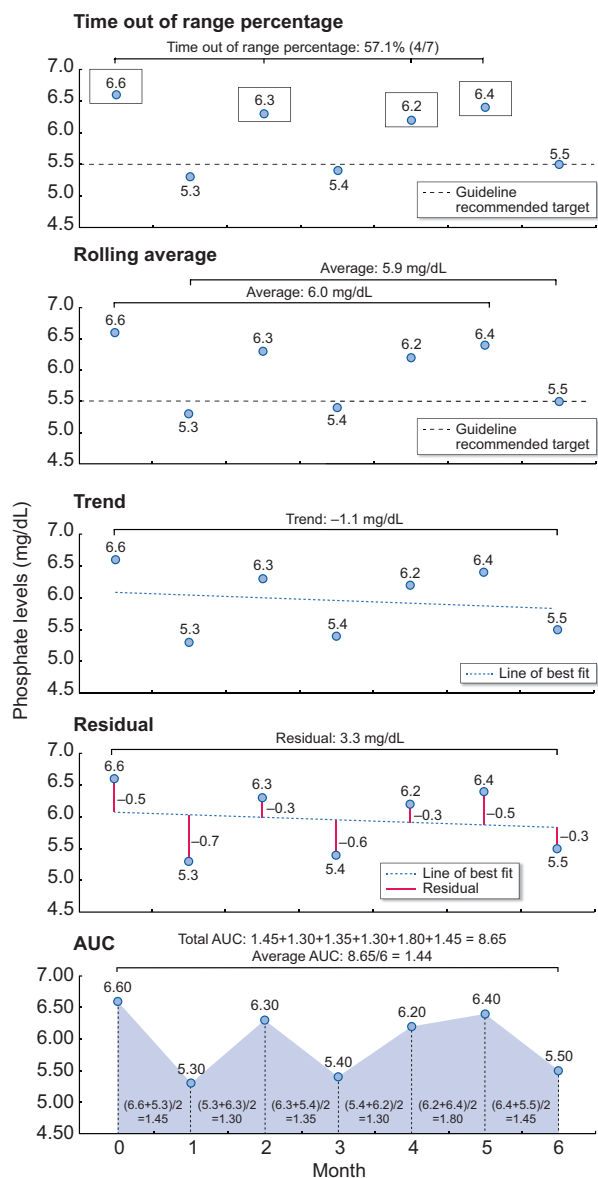
Consistently achieving and maintaining phosphate levels <5.5 mg/dL, let alone more normal levels, is an ongoing clinical challenge [6], and phosphate control in clinical practice has not improved in almost a decade [7]. Novel approaches that more accurately assess phosphate control may allow clinicians to be more responsive to patients’ needs, potentially improving patient outcomes.

## MONTHLY PHOSPHATE DATA ARE NOT A GOOD INDICATOR OF OVERALL PHOSPHATE CONTROL

Although KDOQI guidelines recommend monitoring serum phosphate levels every month following the initiation of dietary phosphate restriction [4], this gives an incomplete picture of phosphate control, e.g. the rate of patients achieving target phosphate levels is much higher when only looking at monthly levels versus results from a longer period [3, 6, 8]. Dialysis outcomes and practice patterns study (DOPPS) data show that in the most recent month, >40% of patients had serum phosphate levels >5.5 mg/dL and >70% had levels >4.6 mg/dL [6]. A chart audit of US nephrology records showed that 42% of patients on dialysis and binders had serum phosphorus levels

>5.5 mg/dL in the most recent month. These rates increase greatly in a 6-month evaluation: 77% of patients on dialysis and binders had serum phosphorus levels >5.5 mg/dL [8], and 91% of patients had levels >4.5 mg/dL on at least one occasion [3]. The challenge is evident within our dialysis unit; in 100 randomly selected patients, almost half had a phosphate value >5.5 mg/dL every month or every other month, and 93% were unable to consistently maintain a phosphate <5.5 mg/dL for the past 12 months. Thus, while ~40% of patients are hyperphosphatemic (>5.5 mg/dL) in any given month, phosphate control over 12 months is erratic, and hyperphosphatemia is frequent. The large discrepancies between these data over different lengths of time show that many patients with hyperphosphatemia may be miscategorized as having ‘well-managed’ phosphate based on a monthly value. These patients may be experiencing the negative effects of hyperphosphatemia because they are not receiving adequate treatment.

A retrospective review of serial phosphate data over a longer time period (e.g. the most recent 6 months) provides a more accurate and complete picture of phosphate control. Whereas reviewing only the most recent monthly lab result provides a ‘snapshot’ without context, reviewing monthly phosphate levels over the past 6 months allows clinicians to see trends, assess patients’ response to treatment, be more responsive to patient needs and make any necessary treatment changes immediately. For example, if a patient’s phosphate levels have been fluctuating in and out of the target range over the last 6 months, clinicians could adjust their phosphate management strategy even if the trend is not consistent. An even more accurate way of evaluating phosphate control over time is the area under the curve method, which shows both how far phosphate is elevated above the target range (2.5–4.5 mg/dL) and how much time was spent with above-target phosphate in a given time period [3]. In addition to being a better predictor of CV mortality than the most recent phosphate level [3], this method also emphasizes that clinicians should take necessary action when a patient exceeds the target phosphate range multiple times in a certain time period, not just when a patient is consistently or consecutively out of range.



**FIGURE 1:** The calculation with the five listed methods with patient's past 7 months' phosphate levels. AUC, area under the curve.

## CLINICAL DECISIONS SHOULD BE BASED ON SERIAL RETROSPECTIVE PHOSPHATE LEVELS

Real-world data support the KDIGO recommendation that treatment decisions be based on serial assessments of phosphate [5]. Implementing new methods of evaluating phosphate would be simple and straightforward, as many methods evaluating lab values that focus on 'trailing' or looking backward are already used in nephrology practices. For example (Figure 1):

- (i). Time out of range percentage: Calculated by dividing the total number of times the patient was out of range over the last 6 months by 6. This method gives a broad picture of how well-managed a patient's phosphate levels are and shows whether a patient is fluctuating in and out of range.

- (ii). Rolling averages over the last 3–6 months: Calculated by dividing the sum of phosphate levels over the last  $N$  months by  $N$ . This method allows easy identification of overall trends (i.e. mean in range or out of range).
- (iii). Trend: Calculated by finding the absolute value of the rate of change or trajectory per month. This method shows how much phosphate levels are changing each month, allowing clinicians to assess trends and response to treatment.
- (iv). Residual standard deviation (SD): Calculated by first drawing a line of best fit for all phosphate values in a given time period and finding the SD of phosphate values from this line. This method shows the magnitude of variability that may be 'hidden' by an average phosphate value.
- (v). Area under the curve (time spent out of range during a 6-month period): Calculated by plotting monthly phosphate levels ( $y$ -axis) against time ( $x$ -axis) and solving for the area of the trapezoid for each month [3]. This method combines how much target levels were exceeded and for how long and has been shown to be a good predictor of CV mortality.

Given the established negative consequences of hyperphosphatemia and the importance of both elevated phosphorus level and time out of range, clinicians should consider shifting their phosphate evaluation approach to a method that takes into account more phosphate levels for potentially better clinical outcomes.

## STATEMENT OF ETHICS

For this review article, no new research study was conducted that prospectively assigns human participants or groups of humans to one or more health-related interventions, and therefore, no patients were enrolled or subjected to therapies. Thus, there are no requirements for any ethical approval or informed consent. The process of developing this article complies with internationally accepted standards for research practice and reporting.

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## AUTHORS' CONTRIBUTIONS

K.J.M. participated in the review and screening of literature, conceptualization, writing and revising of this review article. This work has not been previously published and is not being considered for publication elsewhere.

## CONFLICT OF INTEREST STATEMENT

K.J.M. is a paid consultant for Ardelyx, Inc. and participates in Data Safety Monitoring Board or Advisory Board for Vifor, Tricida and Applied Therapeutics. K.J.M. has no other relevant affiliations or financial involvement with any organization or

entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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