Phosphate Kinetic Models in Hemodialysis: A Systematic Review

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Background: Understanding phosphate kinetics in dialysis patients is important for the prevention of hyperphosphatemia and related complications. One approach to gain new insights into phosphate behavior is physiologic modeling. Various models that describe and quantify intra- and/or interdialytic phosphate kinetics have been proposed, but there is a dearth of comprehensive comparisons of the available models. The objective of this analysis was to provide a systematic review of existing published models of phosphate metabolism in the setting of maintenance hemodialysis therapy.

Study Design: Systematic review.

Setting & Population: Hemodialysis patients.

Selection Criteria for Studies: Studies published in peer-reviewed journals in English about phosphate kinetic modeling in the setting of hemodialysis therapy.

Predictor: Modeling equations from specific reviewed studies.

Outcomes: Changes in plasma phosphate or serum phosphate concentrations.

Results: Of 1,964 nonduplicate studies evaluated, 11 were included, comprising 9 different phosphate models with 1-, 2-, 3-, or 4-compartment assumptions. Between 2 and 11 model parameters were included in the models studied. Quality scores of the studies using the Newcastle-Ottawa Scale ranged from 2 to 11 (scale, 0-14). 2 studies were considered low quality, 6 were considered medium quality, and 3 were considered high quality.

Limitations: Only English-language studies were included.

Conclusions: Many parameters known to influence phosphate balance are not included in existing phosphate models that do not fully reflect the physiology of phosphate metabolism in the setting of hemodialysis. Moreover, models have not been sufficiently validated for their use as a tool to simulate phosphate kinetics in hemodialysis therapy.

Complete author and article information provided before references.

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Hyperphosphatemia, that is, high plasma phosphate concentration, is a well-known electrolyte disturbance in patients with chronic kidney disease. The prevalence is 40-45% in patients with end-stage chronic kidney disease.[1] At this stage, dialysis treatment usually becomes necessary to maintain phosphate concentrations within the normal range. A normal phosphate balance is desirable in dialysis patients in general because it may help prevent severe complications such as vascular calcifications, renal osteodystrophy, and hyperparathyroidism.[2]

Phosphate balance in patients receiving hemodialysis (HD) is usually assessed using a single monthly phosphate concentration obtained before a dialysis session.[3] This value provides a snapshot of the person's phosphate status and informs dialysis prescriptions. However, the method provides only limited insight into the actual phosphate balance. Kinetic modeling is an alternative approach that may yield a more comprehensive understanding of the individual's phosphate balance. Kinetic modeling can serve as a helpful technique to build an understanding of the complexity of biological systems.[4] It is also expected that the method may be applied to describe and predict phosphate behavior when its results are matched against data collected from a patient's blood and dialysate. This matching is essential for establishing exact inorganic phosphate values and prescribing dialysis treatment that prevents phosphate problems. Currently, no phosphate model has gained clinical acceptance, which is presumably due to the complexity of phosphate kinetics. In comparison, urea kinetic modeling is widely used to assess dialysis efficacy.[5,6]

Despite the complex nature of phosphate kinetics, various approaches have been proposed for phosphate modeling within HD therapy.[7-17] However, to our knowledge, a thorough review and comparison of these models has yet to be performed. A review of phosphate models focused on their contents, applicability, and clinical feasibility would inform the current debate about their potential clinical usefulness and inspire further development. Hence, the objective of this study was to review existing phosphate kinetic models with a particular focus on HD therapy. The models are evaluated and compared, and validation procedures are discussed.

Methods

Protocol and Registration

The methodology of this systematic review conformed to review guidelines,[18,19] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement[20] guided the conduct and reporting of this review. The study was registered on PROSPERO (an international prospective register of systemic reviews) as CRD42016050680.

Criteria for Eligibility

All studies of phosphate modeling within HD therapy published before August 31, 2016, were considered. The search was limited to published full-text peer-reviewed journal articles in English that focused on intradialytic or intra- and interdialytic phosphate kinetic modeling. Studies were excluded that focused on only dialytic phosphate removal, peritoneal dialysis, hemodiafiltration (HDF) treatment, hemofiltration treatment, and/or urgent dialysis.

Information Sources

Relevant studies were identified by a comprehensive search in electronic databases and an in-depth scan of key reference lists and other relevant hand searches. Databases included PubMed, Embase, Web of Science, and Scopus. A systematic search protocol formed the basis for the search (see aforementioned PROSPERO registration).

Search

The search was performed in collaboration with a research librarian. Various synonyms, near-synonyms, different spellings, and acronyms were included and combined in order to achieve the fullest possible search. The search was structured and focused using search functions such as Boolean operators, thesaurus, truncation, phrase, abstract/title/keywords, free text, advanced search, etc. To prevent selection bias, a follow-up search was performed before manuscript submission. Item S1 provides the relevant search history from each of the 4 databases, including documentation for the dates last searched.

Selection Process

The selection process comprised 3 steps: (1) removal of duplicates, (2) screening of titles and abstracts for language and relevance of subject matter, and (3) screening of full articles for relevance on the basis of the inclusion and exclusion criteria.

The RefWorks (Refworks, RefWorks-COS, ProQuest RefWorks 2.0, 2010) functions Exact duplicates and Close duplicates were used to remove duplicates. One reviewer (S.H.L.) participated in this phase, whereas 2 reviewers (S.H.L. and O.K.H.) performed steps 2 and 3. Records on which both reviewers agreed were included in the systematic review. Any disagreement was resolved by discussion.

Data Extraction

Two key areas were considered relevant in the data extraction phase: the model approach and the validation approach. The validation approach included 2 areas of interest: the treatment setup and the study design.

For the model approach, the following data were extracted from each study: author, year, model summary, assumptions, number of compartments, included parameters, and comments on strengths and weaknesses. For the validation approach, treatment setup, the following data were extracted: dialysis machine, dialyzer, dialysate specifications, blood flow rate, dialysate flow rate, ultrafiltration (total), vascular access, and dialyzer phosphate clearance. Finally, the data items extracted in relation to the validation approach, study design, included number of test participants, age, sex, number of trials, treatment duration, sampling intervals, key findings, and validation results (residual sum of squares or coefficient of determination [R^2]).

All authors were involved in the data extraction process.

Quality Assessment of Studies

The quality of each included study was assessed using a modified version (Item S2) of the Newcastle-Ottawa Scale.[21] This tool includes 14 quality indicators relating to the appropriateness of the model approach, the treatment setup, and the study design, together with validation of the model and conclusions of the results.

Each study was assessed against the 14 quality indicators and awarded 0, 0.5, or 1 (poor to good) for its quality on each of the 14 indicators. The total of the scores assigned each model study to 1 of 3 categories; low (0-4), medium (5-9), or high quality (10-14). All authors were included in the assessment phase.

Data Synthesis

Studies considered acceptable for inclusion were subjected to narrative synthesis. Different tables were included to summarize the model and validation approaches. In addition, individual quality scores were provided for each study on the basis of the 14 quality indicators (Item S2).

Results

Study Selection

Eleven studies were included for systematic review.[7-17] The 11 studies comprised 9 different phosphate models. Figure 1 provides an overview of the full selection process.

Model Characteristics and Evaluation Approach

Box 1, Item S3, and Table 1 present the included phosphate models. Box 1 provides a summarized overview of the characteristics of the models, Item S3 presents the model structures and equations, and Table 1 elaborates on the model parameters of each approach.

The model approaches included 1-, 2-, 3-, and 4-compartment structures, and the number of model parameters ranged from 2 to 11. All studies agree that the observed mobilization of phosphate requires some kind of generation term. Moreover, in the majority of the studies, the intra- and extracellular compartments were set to be equal to the included compartments.

The validation approach of each phosphate model is summarized in Tables 2 and 3. Table 2 provides information about the treatment setups, and Table 3 provides