Adherence (Part 1) - The challenge of non-adherence in hyperphosphatemia

Phosphate binders have been shown to be effective in regulating phosphorus levels\(^1,2\) and yet according to a recent large observational study,\(^3\) 50% of patients have serum phosphorous concentrations outside the target range. Clinical studies have demonstrated the efficacy of phosphate binders in controlling serum phosphorus and observational studies confirm their widespread use,\(^4\) so to what extent is the difficult of controlling phosphorus levels caused by non-adherence to binder regimens?\(^4\)

**Phosphate binders have shown to be effective at controlling phosphorus levels**

Phosphate binders are widely used in dialysis patients to control phosphate levels and observational studies have shown their use to be associated with improved survival outcomes.

- In a study of 6,797 dialysis patients Cannata-Andia et al. found that patients prescribed phosphate binders had 29% lower all-cause mortality risk and a 22% lower cardiovascular mortality risk.\(^1\)
- Treatment with phosphate binders was independently associated with decreased mortality in an observational study of 10,044 incident dialysis patients.\(^2\)

Despite the widespread use of binders, phosphorus levels in general are poorly controlled, with 50% of patients in a recent study\(^3\) found to have poorly controlled phosphorus levels at baseline. One possible reason for this is the underestimation of the amount of highly absorbable, ‘hidden’ phosphorus in Western diets, which has been shown to be particularly high in processed foods.\(^5\) Alongside this, there is also a growing body of evidence highlighting that many dialysis patients are not adhering to their binder medication.
Evidence suggests patient adherence to phosphate binders is poor

Non-adherence is a problem in many chronic diseases, but can be especially challenging for dialysis patients due to a complex treatment regimen involving both dietary restrictions and multiple medications. Numerous studies have shown that the prevalence of patient non-adherence to phosphate binder treatments is high:

- A survey in 2010 found 76% of nephrologists and 63% of dialysis staff thought non-adherence was the main reason for poor control of phosphorus levels in patients.\(^6\)
- In a cross-sectional study, 502 haemodialysis patients responded to a questionnaire with approximately 70% stating they were non-adherent to phosphate binders.\(^7\)
- A recent study of Spanish dialysis patients found that 60% were non-adherent to their phosphate binder treatment regimens.\(^8\)
- In another study by the same author, results found that in 165 dialysis patients, 40% were non-adherent to their treatments and 21% admitted non-adherence to phosphate binders.\(^9\)
- A systemic review of 34 studies found non-adherence rates averaged at 51% and ranged from 22% to 74%. The result of this review highlighted the variability in measures of adherence.\(^10\)

These data suggest that non-adherence is an important issue in phosphate binder therapy and it is a logical step to suggest that improving these adherence rates could lead to better treatment outcomes for dialysis patients.

This is the first in a series of articles discussing adherence, outcomes & pill burden in hyperphosphatemia. In our next article we will look at associations between adherence and improved outcomes.
References


Adherence (Part 2) - Is adherence to phosphate binder therapy associated with improved outcomes?

Research and clinical experience suggests that adherence to phosphate binders is low, but will improving adherence lead to better outcomes? A meta-analysis of 21 studies, in diseases such as HIV, myocardial infarction and type II diabetes, found that “good adherence to drug therapy is associated with positive health outcomes.”

But does similar evidence exist for adherence to phosphate binder treatment?

Non-adherence is associated with poor control of phosphorus levels

A number of studies have examined the association between adherence to phosphate binders and serum phosphorus levels. From the recent literature:

- Arenas et al. found that haemodialysis patients who were non-adherent to phosphate binders were significantly more likely to have high phosphorus than adherent patients. Non-adherence to phosphate binders was greater than for hypotensive agents, suggesting dialysis patients may have increased difficulty following binder regimens.
- A study of 76 peritoneal dialysis patients found adherence to phosphate binders was greatest in patients with low phosphorus levels. Multivariate analysis showed adherence was the only significant contributor to high serum phosphorus levels.
- In an analysis of 8,616 patients, lower adherence was associated with higher mean phosphorus levels and a lower percentage of patients with serum phosphorus ≤5.5 mg/dL.
- At ASN Kidney Week 2012, Tentori et al. presented an analysis of the DOPPS registry showing non-adherence to phosphate binders was associated with high phosphorus and PTH levels.

Studies such as these suggest that improved adherence may lead to a greater control of serum phosphorus, and a reduced risk of hyperphosphatemia. Given the well-documented links between high serum phosphorus levels and increased mortality in dialysis patients, it seems likely that improving adherence to phosphate binders will have a positive effect on hard outcomes, similar to that seen from improved adherence in other diseases.
Improving adherence may also deliver financial benefits

Poor adherence could also be leading to over-prescription of phosphate binders and a higher pill burden, as physicians escalate their attempts to control high phosphorus levels. This over-prescription also has the potential to increase medication cost. A recent review focusing on the cost of adherence in multiple disease areas concluded that non-adherence is a significant contributor to avoidable healthcare costs in the US, and improving adherence could save “billions of dollars” per year.

But how to improve adherence?

Evidence suggests that improved adherence to phosphate binders could improve outcomes and potentially lower medication costs. But how can clinicians improve adherence? The starting point for this analysis needs to be an understanding of why patients are not adhering to phosphate binders, and this will be the focus of our next few articles on COMPACT Renal.
References


Adherence (Part 3) - Why do patients not adhere to therapies?

A high percentage of dialysis patients do not adhere to their phosphate binder medication, which leads to poor control of serum phosphorus levels. What factors contribute to this non-adherence?

Adherence is a multi-factorial problem

Studies investigating the causes of non-adherence across multiple diseases have found it to be a multifactorial problem. Not only do adherence rates vary between patients, they also vary for the same individual over time and across treatments. In fact, most patients are non-adherent at some point in time. Some of the reasons found for non-adherence to therapies are:

Psychological factors

- Psychosocial factors include patients’ beliefs about their treatment, the amount of social support they receive and even certain personality traits.
- A systematic review of 34 studies on adherence to phosphate binders found that psychosocial factors were the most promising predictors of non-adherence. However, pill burden as a predictor of adherence was not assessed in this review.

Need for lifestyle modification

- One study found adherence to binders to be lowest in patients who had to change their lifestyle in order to adhere.

Cost-to-patient of medication

- In a review of 160 articles, across multiple diseases, on the relationship between treatment costs-to-patient and adherence, increases in patient cost sharing were associated with declines in medication adherence, which in turn were associated with worse health outcomes.

Demographic variables

- Demographic factors such as age, gender, education and ethnicity have all been suggested as factors that can influence adherence.
- However, in a systematic review of studies related to phosphate binders, only age was associated with adherence.
Some factors are particularly relevant to phosphate binder treatment

Two potential causes of non-adherence have particular relevance for patients prescribed phosphate binders.

**High pill burden, combined with regimen complexity**

- Dialysis patients have a high pill burden. One study estimated the average pill burden to be nineteen pills per day, of which phosphate binders contributed about half. Phosphate binder regimens are also relatively complex, involving multiple doses per day administered with meals.
- A recent study has shown that a lower pill burden was associated with greater adherence.
Medication preference and poor tolerability of binders

- One study found that non-adherence to phosphate binders was associated with medication preferences. Perhaps unsurprisingly, patients on a phosphate binder that they did not like showed lower adherence than patients who did like their treatment. 7
- This is a particularly significant factor in haemodialysis patients as many binders have relatively poor tolerability over time, with patient-reported side effects a common reason for binder discontinuation. 8

Both tolerability and pill burden appear to be practical, modifiable targets for improving adherence in hyperphosphatemic patients. We will examine these issues in greater detail in our next articles.

References


Adherence (Part 4) - Why do patients not adhere to phosphate binders: poor tolerability?

Poor drug tolerability may be a reason why more than half of dialysis patients, on average, do not adhere to phosphate binder medication. With the range of available phosphate binders likely to expand in the next year, physicians may be able to improve adherence by selecting more appropriate binders for their patients.

A recent paper by Wang et al. identified poor toleration of side-effects as a major reason for discontinuation of phosphate binder treatment. In this study, 30,933 patient records were retrospectively analysed to assess the reasons behind phosphate binder discontinuation. 50% of records did not contain a reason for discontinuation and 27% of discontinuations were due to “lab results”. In this latter category, hypophosphatemia (42%) and hypercalcemia (24%) were the largest attributed causes of discontinuation due to lab results.

11% of discontinuations, the next largest cohort, were due to “patient not tolerating” and further analysis of this group presented some interesting findings. Nearly 48% of these patients discontinued therapy due to gastrointestinal upset and there was noticeable variation in the reasons for discontinuation between specific binders.

Poor tolerability of binders may be a modifiable cause of non-adherence

While discontinuing therapy, and noting this in the patient record, does not equate to non-adherence, there is likely to be a high degree of overlap between the two factors.

Results from a cross-sectional study of approximately 500 patients support this relationship between adherence and tolerability. Almost 15% of patients who were classified as non-adherent in this study (and approximately 6% of those classified as adherent) reported that they always or almost always stopped taking phosphate binders on their own initiative after “feeling worse”.

This intentional non-adherence to therapy may be modifiable with closer consideration of the side effects of particular binders. The Wang et al. study highlights some factors that clinicians may wish to consider when selecting a phosphate binder for an individual patient. Such individualization of treatment could be rewarded with increased medication adherence and, potentially, improved outcomes. This process is also likely to be supported in future by a wider range of available therapy options, with different tolerability profiles.
References


Adherence (Part 5) - Why do patients not adhere to phosphate binders: high pill burden?

Pill burden is recognized as a factor that can affect adherence in a number of diseases, such as HIV. For dialysis patients, the daily pill intake is very high, with a large proportion of this burden comprised of phosphate binders. Given that non-adherence to phosphate binders is common, is there evidence that shows a direct association between pill burden and adherence in dialysis patients?

Studies show that high pill burden affects adherence in phosphate binder treatment

In a cross-sectional study of 233 US dialysis patients, Chiu et al. found that 62% of patients were non-adherent and adherence decreased significantly with pill count. The study results also suggested that low adherence could lead to over-prescription of phosphate binders and so to a greater pill burden. This clinical approach potentially creates a self-fulfilling, repeating cycle of low adherence, poor phosphorus control and dose escalation.

PHOSPHATE BINDERS MAKE UP A LARGE PROPORTION OF THE PILL BURDEN FOR HD PATIENTS

- Daily pill burden in HD patients is one of the highest reported in any chronic disease state (~19 pills/day)
- Median pill burden is ~9 pills/day for phosphate binders

Importantly, overall pill burden was associated with a low physical component summary score of the SF-36 QoL (Quality of Life) assessment. Increasing the number of pills prescribed did not improve control of serum phosphorus levels and further reduced the patient’s quality of life assessment.\(^2\)

Recently, Wang et al also found that increasing pill burden was associated with non-adherence, and non-adherence in turn was associated with poorly controlled serum phosphorus levels.\(^3\) Using data from a pharmacy management program, the investigators tracked dialysis patients on phosphate binder monotherapy over time. 8,616 haemodialysis patient records were analysed, and their medication possession ratio (MPR) and pill burdens were calculated.

The Medication Possession Ratio is the proportion of days the patient has sufficient medication available to have taken the medication as prescribed. It is commonly used as an indirect measure of adherence, with a low MPR implying low adherence. An MPR of 100% would suggest perfect adherence.

The Wang et al. study found that:

- Weighted MPR levels were low overall, ranging from 51% to 42% in different cohorts,
- MPR increased as pill burden decreased, with adherence strongest (51%) in the group with the lowest pill burden (0-3 pills per day), and
- Higher MPR was associated with worse control of phosphorus to target ranges.

These results suggest that a lower pill burden results in greater adherence and lower phosphorus levels. The MPR levels of 40% to 50% align well with other real-world, medication adherence data, lending eight to this observational study.

While high pill burden is only one of several factors that may be contributing to poor adherence in dialysis patients, reducing this pill burden is a practical and achievable goal. Switching the type of binders used in patients to those which require less pills per day may deliver some of the improvements in adherence and outcomes that clinicians are seeking.
References


Adherence (Part 6) - Improving adherence through treatment optimization and simplifying regimens

Patients can find it challenging to adhere to complicated treatment regimens. For example, elderly patients who have cognitive or memory impairments may find therapy compliance difficult,¹ and younger patients may struggle to adapt their lifestyle to treatment demands.² This article will look at different ways in which treatment strategies can be adjusted in order to reduce regimen complexity and potentially improve adherence.

Simplifying dosing demands

Kripalani et al. analysed 37 randomized controlled trials, across multiple chronic diseases, which described interventions intended to enhance patient adherence to self-administered medications. The review found that the most effective approaches were behavioural interventions that simplified dosing demands.³

A systematic review of 76 studies also showed that simpler, less frequent dosing regimens are associated with better adherence in a variety of diseases.⁴ Similarly, a Cochrane Review of hypertensive patients also found that reducing the number of daily doses increases adherence.⁵

However, reducing the frequency of phosphate binder dosing is particularly challenging as pills must be taken at every meal. Despite this it may be possible to:

1. Reduce the number of phosphate binders that need to be taken at each meal, and
2. Rationalize the dosing regimens of binder and non-binder medications, for example by equating a “morning” dose to “with breakfast”.

Reminder systems

A randomized clinical trial found that a personalized cell phone reminder system was capable of improving adherence to antiretroviral therapy in 23 HIV patients.⁶ Similarly, a Cochrane review of interventions to improved adherence to lipid lowering drugs found that the most effective interventions were based on reminder systems.⁷

Dose packaging strategies

A systematic review of the adherence benefits of packaging pills with a calendar and/or pill organisers found that six out of ten trials reported higher adherence. However in only one study did this relate to clinically significant improvement.⁸
Individualized treatment plans

Healthcare professionals can also draft specific treatment plans for patients. A Cochrane review by Gray et al. showed that individualized care planning improved adherence in glaucoma patients. Personal treatment plans may also have greater importance in patients with multiple comorbidities, where each condition has its own treatment regimen. Pharmacists have an increasing role to play in developing these plans, through programs such as Medicare’s Medication Therapy Management.

References


Adherence (Part 7) - Improving adherence through increased patient education

Educational interventions have been found to increase adherence in multiple diseases, although reported effects have been inconsistent and studies have largely been short-term. In this article we review whether patient education can similarly improve adherence to phosphate binder medication.

Educational programmes can improve patient adherence

Several studies have shown that educational sessions or programs regarding phosphate management have led to improved adherence and/or treatment outcomes.

- In a randomized controlled trial of 56 dialysis patients, those who attended one-to-one teaching sessions, aimed at improving patients’ knowledge of phosphate management, showed a significant reduction in serum phosphorus concentrations compared to control.

- Gardulf et al. studied 43 CKD patients (most on dialysis) attending a 2-month educational program regarding calcium and phosphate balance, food intake and phosphate binders. The group exhibited significantly reduced plasma phosphate for up to 12 months afterwards.

- A nurse-led educational and counselling session provided to 41 patients on phosphate binders resulted in an increase in adherence from 83% to 94% after 13 weeks. The control group’s adherence decreased from 86% to 76%.

- Another nurse-led education program over 12 weeks saw a significant improvement in the proportion of patients who took their phosphate binder correctly, increasing from 44 to 72%, although this did not lead to a statistically significant change in clinical markers.

- A “Phosphate Education Program” in children with CKD used ‘phosphorus units’ to allow patients to quickly estimate phosphorus content in foods and self-adjust binder dosing. Within 6 weeks after training, the percentage of children with serum phosphate outside of the target range dropped from 63% to 31%.

While these studies suggest benefits from patient education regarding phosphate management, there is a clear need for a randomized controlled trial evaluating educational interventions over an extended period. This is in line with a 2008 Cochrane Review of interventions for enhancing adherence across multiple conditions, which concluded that “high priority should be given to fundamental and applied research concerning innovations to assist patients to follow medication prescriptions for long-term medical disorders.”

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Patients would like more information about phosphate management

This need for further research is especially apparent when we consider patients’ current levels of understanding about their treatment goals. In one study, 84% of surveyed patients had heard of phosphate, but 42% were unsure of high phosphate foods and 46% were unaware of consequences of elevated phosphate. This Australian study also revealed an interesting symmetry between patients and nephrologists:

- 74% of patients wanted to know more about CKD-MBD (40% via written material).
- 84% of nephrologists believed that their patients wanted to know more about CKD-MBD, but
- Only 28% provided written patient materials on CKD-MBD.

Adherence to phosphate binders: a quick summary

We have reviewed the topic of adherence over the past few weeks on COMPACT Renal. In summary:

- Adherence to phosphate binder therapies in dialysis patients is poor, with approximately half of patients non-adherent
- Non-adherence to phosphate binders is associated with poor control of serum phosphorus which is associated in turn with worse disease outcomes
- While non-adherence is a complex, multifactorial problem, there are a number of potentially modifiable factors that clinicians could address in order to improve compliance
- Reducing pill burden and optimizing therapies to improve tolerability are two possible approaches that may bring specific benefits in dialysis patients
- Simplifying dosing regimens and improving patient education may also lead to improved medication adherence
References


Adherence (Part 8) – CompAct expert view: Dr Stuart Sprague on the importance of low pill burden in the treatment of hyperphosphatemia

In a new video interview for COMPACT, Dr Stuart Sprague from the University of Chicago discusses the optimal approach to phosphate management in dialysis patients. Dr Sprague highlights that effective, tolerable, and low pill burden phosphate binders are key to patient adherence in this highly medicated patient population.

Transcript

Hello, I'm Dr Stuart Sprague. I'm currently at North Shore University Health Systems and on the faculty at University of Chicago Pritzker School of Medicine.

I'd like to take a few minutes right now and talk to you about the optimal, integrated approach towards phosphate management in dialysis patients.

I'm sure we all realize that regulating serum phosphate is very important for a patient's optimal health and outcome, and it's become a very difficult aspect for many patients to do. Generally, the integrated approach toward phosphate management includes:

• Dietary counselling and the restriction of foods that are high in inorganic phosphates, without excessively restricting protein.

• The use of adequate dialysis.

• The appropriate use of medication, such as vitamin D compounds so we don't enhance phosphate absorption.

• Appropriate management of parathyroid hormone and adequate dialysis.

However, the mainstay and probably the most important feature of taking care of these patients is that of using phosphate binders.

When we want to approach phosphate binders, we want to make sure that they have low GI side effects, that patients do tolerate them, and that they're able to take them with their meals, and probably one of the biggest aspects is that of patient compliance and adherence, [which is related to] the number of phosphate binders the patient has to take.
If we consider that many dialysis patients take well over 20 pills a day, and frequently half of those pills are phosphate binders, we then can appreciate how difficult it may be for patients to become compliant or adherent with their phosphate binders, as it becomes difficult to take 2, 3, or 4 pills with each meal, especially these pills that affect the taste of the meal in a negative way.

So therefore, patient adherence and compliance is something that we have to accomplish by using phosphate binders that are effective, tolerable, and require a low pill burden. Having patients having a low pill burden will then enhance their ability to take these binders as prescribed.