HYPOPHOSPHATEMIA AFTER KIDNEY TRANSPLANTATION

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Abstract

Serum phosphate level falls, not uncommonly to really low level (<0.32mmol/l), after successful renal transplantation. Re-distribution of phosphate between intracelluar and extracellular compartments, osmotic diuresis and renal phosphate loss under the influence of high parathyroid hormone level are the main mechanisms for the development of hypophosphatemia in early post-transplantation period. The short-term and long-term consequences of post-transplantation hypophosphatemia are unconfirmed. In the present retrospective study, the changes of serum phosphate over first twelve months after renal transplantation were followed in 30 new renal-transplant recipients. Seventy percent of renal transplant recipients (21 out of 30) had hypophosphatemia (<0.8 mmol/L) detected. The first trough serum phosphate level was observed at the third and fourth weeks after transplantation. High serum phosphate level prior to transplantation was the single factor associated with post-transplantation hypophosphatemia. No predictors of serum phosphate

levels after renal transplantation were found. No complications of hypophosphatemia, regardless of whether phosphate supplementation was given, were observed in the present study. The dilemma of treating hypophosphatemia and various treatment modalities after renal transplantation will then be discussed.

Introduction

Hypophosphatemia is an electrolyte disturbance commonly found in early post-transplantation period [1-6] and it not uncommonly persists more than one year after renal transplantation [7-9]. The severity of hypophosphatemia varies from patient to patient. In non-renal transplant recipients, acute complications of severe hypophosphatemia, defined as <0.32mmol/l, are well-reported in patients with underlying medical condition such as alcoholic, hyperalimentation, and diabetic ketoacidosis [10,11]. An acute complications including rhabdomyolysis [10], red cell dysfunction [10], leukocycte dysfunction [10], platelet dysfunction [10], central nervous system dysfunction [10,12-13], respiratory failure [12,14], cardiac dysfunction [15-16] and hemolytic anaemia [17] have not been reported in renal transplant recipients during early post-renal transplantation period. However, persistent hypophosphatemia has been implicated in the development of osteomalacia in those with [7] and without renal transplant [18-19].

The approach to correct the hypophosphatemia trying to avoid the acute complications and late effects of hypophosphatemia is commonly practiced in many renal transplant centers. The dosage of phosphate replacement is not unified. As an intracellular anion, the serum

phosphate level correlates poorly with the body stores [10]. The depletion of body phosphorus or the intracellular phosphate, rather than hypophosphatemia, is the crucial determinant of all complications of hypophosphatemia [10]. Nevertheless, the measurement of body phosphorus store is inaccessible. Treatment of post-transplant hypophosphatemia is thus based on the discretion individual physicians or centers. Guidelines for treating this situation are poorly defined. However, phosphate supplementation in post-renal transplantation recipients runs the risk of delaying the recovery of secondary hyperparathyroidism [6].

In the following retrospective study, the change in serum phosphate levels over time was analyzed in a group of new renal transplant recipients. They were studied in the first year post-transplantation. Different potential factors affecting the trough serum phosphate levels were studied. The clinical outcomes of patients with or without phosphate supplementation were then compared.

Patients and Methods

From the 34 patients who had undergone renal transplantation during the period from January 1999 to December 2000, 30 patients were recruited in this retrospective study. Three patients were excluded because of major illness occurring in first-year post-transplantation (one had gram negative septicemia, one had tuberculosis infection of the graft ureter and one had repeated intestinal obstruction). The fouth patient was excluded because she had total parathyroidectomy performed before transplantation.

At the time of renal transplantation, they had been on dialysis for a mean period of 20 ± 5 months (range 0-120). The maintenance immunosuppression therapy consisted of prednisolone, cyclosporin and azathioprine or mycophenolate mofetil. When the patients returned to us from the transplantation centers in Mainland China, the first available serum phosphate level was obtained at variable interval (3.1 ± 0.3 weeks) after transplantation. The serum creatinine upon presentation to our unit was 133 ± 30 μmol/l (range 97 to 198). They had been taking diet containing 800-1200mg phosphorus daily, as assessed by our dietitians.

Study Protocol

All patients were followed up twice weekly for the first 4 weeks, once weekly in the 2nd month, once fortnightly in the 3rd and 4th month, once a month in the 5th and 6th month, once every 6 weeks in 7th and 8th month, then once bimonthly in the subsequent months post-transplantation. The immunosuppressive therapy was adjusted in each individual patient based on our center's protocol.

Serum phosphate levels (normal range of our laboratory: 0.8-1.5 mmol/L) were measured at each clinic visit. Additional measurement of serum phosphate level would be performed at the discretion of the attending doctors. The weekly mean serum phosphate level was followed in the first year post-transplantation. **Trough phosphate level (Trough-Pi)** was the first detectable lowest value of serum phosphate after transplantation. **Time to recover from Trough Pi** was defined as the time required for the serum phosphate level to rise from trough Pi to normal level that persisted for 2 weeks. **Pre-transplantation phosphate level** was the mean of serum phosphate level over 3 months prior to transplantation. Similar calculation was used to determine the pre-transplantation calcium and alkaline phosphatase level.

Pre-transplantation intact parathyroid hormone (PTH) level, measured by Immulite automated immunoassay analyzer (normal range 1.1-5.7 pmol/L), was the latest measurement done within 12 months prior to transplantation. **The slope of PTH level vs time** was the rate of change of PTH level within 12 months prior to and after renal transplantation, using all available PTH measurements.

Oral phosphate mixture starting at 10ml tds (each ml contained 0.567 mmol sodium and 0.315mmol phosphate) was prescribed to some of the hypophosphatemic patients as determined by the physicians. Once prescribed, the dose of it would be titratted according to the serum phosphate level. It would usually be stopped when the serum phosphate level was normalized consecutively for more than 2 weeks.

Three groups of patients were identified in the present retrospective study. **Group [N-Pi]** included normophosphatemic patients in the fifty-two weeks after transplantation. **Group [H-PiS]** included hypophosphatemic patients given oral phosphate supplement at any time during the study period. **Group [H-Pi]** included hypophosphatemic patients without oral phosphate supplement.

The outpatient records and hospital notes were reviewed carefully to obtain any documentation of symptoms attributable to hypophosphatemia. These clinical data were followed for the first year post-transplantation.

Statistical analysis

The values of parameters were given as mean (± standard error of mean) where appropriate. Linear regression analysis was used to estimate the rate of change in PTH level for each patient using all the available pre-transplantation and post-transplantation PTH values. Differences between the groups were assessed by non-paired Mann-Whitney *U* test where appropriate. Using backward stepwise selection method, linear multiple regression models were used for multivariate analysis, with possible predicting factors first identified by correlations using Spearman correlation coefficient. Statistical significance was assumed at a *P* value less than 0.05 (two-tailed).

Results

The demographic data of 30 patients was shown in **Table 1**.

Time to first Trough-Pi after transplantation

The time to the first detectable Trough-Pi was shown in **Figure 1**. Eighteen patients (60%) had the first detectable trough value between the third and fourth week post-transplantation.

Trend of serum phosphate level over first 52 weeks post-transplantation

Seventy percent (21 out of 30) of renal transplant recipients had experienced hypophosphatemia during the first year after transplantation. The changes of mean serum phosphate level [**Pi**] over the first 52 weeks post-transplantation in all 30 recipients was shown in **Figure 2**. The trough Pi level occurred at 2^{nd} to 4^{th} week post-transplantation. Nearly all patients became normophosphatemic at 6 months post-transplantation. No patients were hypophosphatemic after one year post-transplantation.

When these thirty renal transplant recipients were divided into 3 groups; Group [N-Pi], [H-PiS] and [H-Pi], the changes in serum phosphate level over first 24 weeks after transplantation in the later two groups were similar (**Figure 3)**.

Factors associated with post-transplantation hypophosphatemia

The pre-transplantation serum phosphate level was significantly higher in hypophosphatemic patients than in the normophosphatemic group (2.31 ± 0.09 v.s. 1.37 ± 0.17, P <0.05). There were, however, no other biochemical parameter to distinguish the two groups (**Table 2)**.

Outcome of oral phosphate supplement in hypophosphatemic patients

There was no significant difference in the time to recover from trough Pi between [H-PiS] and [H-Pi] patients (**Table 3)**. The two group had similar rate of drop in PTH level over the twelve-month period. No complication of hypophosphatemia was observed in all twenty-one hypophosphatemic patients.

Cross-sectional analysis of the whole cohort of 30 patients

Using backward stepwise selection method and with possible predicting factors first identified by univariate analysis, linear multiple regression revealed no significant predictors of serum phosphate level (factors included serum phosphate, calcium, alkaline phosphatase and PTH levels, duration of dialysis before transplantation and the cumulative dose of steroid after transplantation).

Discussion

The importance of phosphorus is exemplified by its distribution within body. For a 70-kg man, there is approximately 23,000mmol (712gm) of phosphorus [10]. Eighty percent of the body phosphorus is present in the bone which complexes with calcium to form hydroxyapatite for proper mineralization of the skeleton and another nine percent is present in the skeletal muscle. Serum phosphate is regulated within a relatively narrow range (0.8-1.5mmol/l). Plasma phosphorus consists of phospholipids, ester phosphate and inorganic phosphates which are completely ionized, circulating as HPO_4^{2-} or H_2PO^{4-} in the ratio of 4:1 at a plasma pH of 7.40. The intracellular content is 40 times greater than the extracellular compartment. Most of the intracellular phosphorus is stored in its organic form as an intermediate substrate of protein, lipid and carbohydrate formation. A small proportion is present as inorganic form, which is important for ATP re-synthesis. Clinical abnormalities of hypophosphatemia are related to the intracellular depletion of ATP [10,44]. Therefore, the intracellular content of phosphate is much more important than the serum phosphate level in regulating various cellular functions.

Homeostasis of phosphate depends on balance between gastrointestinal absorption and renal excretion of phosphate. Phosphorus is present universally in plants and animal. A traditional Chinese diet contains adequate daily requirement of phosphorus (800-1600 mg/day). It is primarily absorbed in the jejunum and ileum in proportion to food phosphate content [20]. Seventy percent of the ingested phosphorus is absorbed. Active absorption of phosphorus by a Na-dependent co-transporter is demonstrated in rats' intestine [31]. The mechanism for phosphorus absorption in human is uncertain though vitamin D can increase the intestinal uptake of phosphorus [21]. Ninety percent of the absorbed phosphorus is excreted through the kidney while the last ten percent is excreted into feces. Nutritional deficiency or malabsorption of phosphorus is a rare cause for hypophosphatemia.

As ninety-five percent of serum phosphate is freely filtered in the glomeruli, renal handling of the phosphate is of paramount importance in altering the serum phosphate level and regulation of the total body phosphate content. Under normal situation, eighty percent of the filtered phosphate is reabsorbed in the convoluted and straight segments of the proximal tubules [22]. The initial step in renal phosphate reabsorption is the movement of the type II Na/Pi cotransporter from the lumen of

proximal tubule across the microvillar brush border membrane into the tubular cell [23]. This transport is probably the rate-determining step for phosphate reabsorption in the proximal tubules. The activity and number ,and thus the capacity, of the Na/Pi co-transporter is modulated by numerous factors including dietary phosphorus content, hormones and metabolic factors (**Table 4)**.

Previous observations showed that phosphaturia occurred when there was an increase in extracellular fluid volume [29], decrease in serum calcium level [30], acute respiratory alkalosis [32], acute metabolic alkalosis [32], osmotic diuresis [33], glucose loading and glycosuria [33]. These metabolic effect on phosphate excretion may represent the inhibitory effect of various hormone listed above on the renal Na-Pi cotransporters.

A true phosphate-regulating hormone has not been identified so far [24]. Parathyroid hormone, a well-known hormone that alters the serum and renal excretion of phosphate, is mainly serving to control the serum calcium level rather than phosphate level (**Figure 4**). Specific system responsible for controlling deficit or excess of body phosphate is mysterious. But judging from the ample intracellular content of phosphate in bone and muscle, the unidentified system should respond to the metabolic needs or growth rather than extracellular concentration.

The etiology for post-transplant hypophosphatemia is multi-factorial. Renal transplantation is the most effective way in correcting phosphate retention of chronic renal failure. When the allograft starts to function, osmotic diuresis from high concentration of urinary urea and creatinine, high circulating PTH level, increased ECF volume from peri-operative fluid supplementation all stimulate renal phosphate loss. Moreover, the phosphaturic effect of steroid and azathioprine [3] will decrease the serum phosphate level further. On the other hand, restoration of normal production of endogenous of 1,25-dihydroxycalciferol [34-36] will counteract phosphaturia by suppressing hyperparathyroidism. Resumption of normal to high phosphate diet will help to replace the body store of phosphorus. To make the situation more complicated is the shift of phosphate between different body compartments, e.g. from serum to bone, when there is involution of the hyperparathyroidism after successful renal transplantation.

Consequently, a rapid change in serum phosphate, sometimes to the degree of severe hypophosphatemia, can be seen in the early post-transplant period when the allograft starts to function well. It does not necessarily mean that the body is phosphate-deficient as the homeostasis of phosphate is operating together with phosphate retention before transplantation.

The development of post-transplant hypophosphatemia is expected to vary a lot from patient to patient as a result of different immunosuppressive and antacid therapies. Hamper et al [2] reported in 1969 that one fourth of their patients (n=150) with good graft function had serum phosphate level <0.4mmol/l in the first 3 to 6 months post-transplantation. At that time, the renal transplant recipients were taking steroid, azathioprine and aluminium hydroxide, the latter used as anti-ulcer prophylaxis. Higgins et al [3] found that there was two separate periods of hypophosphatemia over 12 months post-transplantation in 72 recipients with good graft function (serum creatinine 75-150μmol/l). The first trough phosphate level occurred in the first 10 days post-transplantation while the second trough level, the lowest value, occurred between 30 to 40 days post-transplantation. The variation of the serum phosphate level was found to be independent of serum creatinine. They suggested that the first trough level was related to the residual effect of the phosphate binders and the insufficient endogenous production of 1,25-$(OH)_2$-Vitamin D. Therefore, the immediate post-transplantation period might not be the appropriate time to study the effects of various factors on serum phosphate level. Serum phosphate level measured between Day 21 to 77 post-transplantation was significantly lower in patients taking prednisolone and azathioprine than those on cyclosporin

alone. We did not have the serum phosphate levels in most of our patients in first 2 weeks post-transplantation, the presence of 2 separate trough values would not be demonstrable in present study. Our finding of trough phosphate level at the third or forth week after transplantation echoes the findings of Higgins et al [3]. Hypophosphatemia did not persist after the 20 and 24 weeks post-transplantation in Higgin's and the present studies respectively

Factors associated with a low serum phosphate level in the post-transplantation period have not been studied before. Pre-transplantation hyperparathyroidism is believed to be the most important determining factor of post-transplant hypophosphatemia. This theoretic association could not be demonstrated in the present retrospective study. Small sample size and the possibility of type I statistical error is a distinct possibility. PTH level could not be obtained at or near the time of transplantation when they only presented to us a few weeks after operation. Therefore the pre-transplant PTH in present study might not reflect the true severity of hyperparathyroidism at the time of transplantation. However, we have demonstrated that pre-transplant hyperphosphatemia was associated with post-transplant hypophosphatemia. This finding is consistent with the hypothesis that

hyperparathyroidism is related to the development of post-transplantation hypophosphatemia.

The complications of hypophosphatemia in renal transplant recipients appear to be uncommon. Lotz et al noted the symptoms of malaise, anorexia and weakness in 3 subjects, one hypoparathyroid, one pseudohypoparathyroid and a normal people when their serum phosphate level was induced to drop below 0.32mmol/l by taking aluminium hydroxide and magnesium-aluminium hydroxide orally [17]. He concluded that this represented phosphorus-depletion syndrome. However, these symptoms can be regarded as rather non-specific in renal transplant recipients. They might have well tolerated to the uremic symptoms of malaise, anorexia and weakness. They may even ignore these without reporting to the physicians. Moreover, weakness and malaise could be the results of steroid therapy [37]. The frequent occurrence of CMV infection in the post-transplant period will also mask the presentation of hypophosphatemia when they experience similar constitutional upset. Adverse effects of severe hypophosphatemia were not detected in 72 renal transplant recipient in Higgins' series. Moreover, all cases of hypophosphatemia resolved spontaneously. One of our patients had a sudden drop in serum phosphate down to 0.2mmol/L at the time of CMV infection. Hypophosphatemia resolved spontaneously with

phosphate supplement after CMV infection had been controlled. In the literature, all those life-threatening complication of hypophosphatemia occurred in patients who were prone to develop phosphate depletion [10-11, 13-16]. It remains unknown whether the management of post-transplant hypophosphatemia should deviate from that in patients with other medical conditions.

The benefits and drawback of treating hypophosphatemia in early post-transplant period allure a lot of interest. Oral phosphate supplementation is a common practice in treating post-transplant hypophosphatemia. Ambuhl et al studied the outcome of hypophosphatemic renal-transplant recipients with and without oral phosphate supplement at one month post-transplantation [5]. All patients had optimal graft function. The serum phosphate concentration was normalized within 2 weeks after phosphate supplement. However, regardless of the supplementation, serum phosphate concentration rose to normal within 12 weeks of observation (i.e. at 4 months after renal transplantation). The serum calcium and PTH level were not altered during the study period. Therefore, oral phosphate supplementation given in the early post-transplantation period provided a faster correction of hypophosphatemia than in spontaneous recovery. However, there has been no report of adverse sequel when the

hypophosphatemia was left untreated. In the present retrospective study, the duration of hypophosphatemia was unaltered by oral phosphate supplementation and there was no complication of hypophosphatemia found in the untreated group of patients. These results echo Ambuhl et al's findings [5]. We may not need an early rise in serum phosphate if there is no harm to leave it untreated in the early post-transplant period.

Drawback of oral phosphate supplementation has been observed when it was given to hypophosphatemic renal-transplant recipients at more than 6 months after transplantation [6]. Caravaca et al confirmed that there was a significant increase in PTH concentration when daily oral phosphate supplement of 1.5gram was given for 15 days in hypophosphatemic renal transplant recipients. All subjects had creatinine clearance greater than 46 min/min/1.73m^2. There was significant increase in serum phosphate level after this short duration of phosphate challenge. The resultant metabolic disturbances included a significant drop in 1,25-$(OH)_2$-Vitamin D and serum calcium levels but a significant rise in serum PTH concentration. These changes might have potential negative impact on the regression of pre-existing hyperparathyroidism. When the patients were subdivided into two groups; those with CrCl > 70m/min/1.73m^2 and others with CrCl between 46 and 69 ml/min/1.73m^2. A similar increase in PTH level was demonstrated in both groups irrespective of CrCl. Therefore, the

injudicious use of oral phosphate mixture, even short-term, based on low serum phosphate level may potentially do more harm than benefit in renal transplant recipients in the early post-transplant period.

Suppression of the residual hyperparathyroidism is a logical way of correcting post-transplant hypophosphatemia. On one hand, it can replace the deficient 1,25-$(OH)_2$-Vitamin D activity in early post-transplant period. On the other hand, it can suppress the pre-existing hyperparathyroidism and so the serum phosphate level is expected to rise after treatment. Furthermore, calcitriol has been shown to have direct inhibition on the renal Na-Pi cotransporter [26] resulting in renal conservation of phosphate. An increase in intestinal uptake of phosphorus in animal has been noted after calcitriol therapy [21]. Steiner et al [4] tried daily 1,25-$(OH)_2$-Vitamin D (range 0.25-1.00μg /day) or dihydrotachysterol (range 0.13-0.63 mg/day) together with calcium 1.0 gram on 10 hypophosphatemic renal-transplant recipients for an average period of 8 weeks. They were at 2-9 months post-transplant with mean serum creatinine 126 ± 18μmol/l. The dose of vitamin D was adjusted according to serum calcium levels. There was significant drop in PTH level and requirement of oral phosphate supplement while the serum phosphate concentration rose significantly at the end of study. One of the patient (10%) had hypercalcemia and 2 patients had hypercalciuria (20%)

requiring dosage reduction of calcium. The use of calcitriol in treating post-transplant hypophosphatemia carries dual benefits but there is a definite risk of hypercalcemia. Thus frequent monitoring of serum calcium level is required.

A distinct clinical entity of isolated renal phosphate wasting [7-9] should be re-visited. The affected renal transplant recipient will have isolated persistent hypophosphatemia from renal phosphate loss more than one year post-transplant. The parathyroid activity is normal. The excretion rates of other substances reabsorbed in the proximal tubule such as uric acid, glucose and amino acids, are normal. Calcium infusions sufficient to decrease the PTH concentration do not reduce the urinary phosphate excretion [39]. It is implicated in the development of osteomalacia in renal-transplant recipients [7]. As the musculoskeletal system of renal transplant recipients have already been exposed to a multitude of insults [38] and chronic renal phosphate loss can lead to urolithiasis [40], correction of the persistent renal phosphate wasting may be beneficial. Graf et al [8] demonstrated that there was a significant increase in serum phosphate concentration with concomitant increase in the tubular reabsorption of phosphate (increase in TmP/GFR) after 1α-hydroxycholecalciferol at a daily dose of 1μg taken for 3 weeks. The serum PTH activity and calcium level were found to be unaltered.

Therefore, short-term use of 1α-hydroxycholecalciferol is effective in managing isolated renal phosphate wasting but its complications, namely hypercalcemia and hypercalciuria, in long-term use have not been tested,.

Dipyridamole has been demonstrated to reduce renal phosphate wasting in non-renal-transplant recipients [41-42]. By taking dipyridamole 75mg Qid orally for one year, serum phosphate returned to normal and the tubular reabsorption of phosphate increased [42]. These beneficial effects started at 3 months and were plateau at 9 months post-treatment. The changes were reversible after stopping dipyridamole. Serum PTH and calcium levels were kept unchanged during the first year of treatment. Minimal interference of dipyridamole on the PTH and calcium homeostasis made it an exciting drug to try in post-transplant hypophosphatemic patients, either in early or late transplant period. However, Prie et al [42] had shown a significant decrease of 1,25$(OH)_2$vitamin D level at the end of study. Therefore, though not confirmed by any clinical trial, delaying the regression of secondary hyperparathyroidism is a potential drawback if it is used in early post-transplant period.

Serum phosphate level is a poor indicator of depletion in body phosphate or intracellular phosphate [10]. ^{31}P nuclear magnetic resonance

spectroscopy (NMR) of skeletal muscle has been used to detect the intracellular orthophosphate content. From a study on NMR spectroscopy, the percentage change in the concentration of intramuscular phosphate is lower than that is in plasma [43] in hypophosphatemia. Even though the plasma concentration spans a fourfold range (0.5-2.0 mmol/l), the corresponding intramuscular phosphate concentration increases by 70% only. This discordance between intramuscular phosphate content and serum phosphate concentration is further demonstrated by the study performed by Higgins et al [3].

A sensitive and specific marker for detecting depletion in body Pi or intracellular Pi content will certainly help us solve the dilemma of treating hypophosphatemia. However, there is virtually no such marker available. Platelet nucleotide studies have been proposed to be a rapid and sensitive test for identifying phosphate depletion by Goodman et al [36]. In this test, the ability of platelets to synthesize C^{14}-ATP from added C^{14}-adenosine and appreciable amounts of hypoxanthine is measured by spectrometer and is compared between hypophosphatemic and normal subjects. Goodman et al demonstrated that a reduced ability to produce ATP from its precursors was found in a phosphate-depleted patient. However, its validity has not been test in large-scale study.

Conclusion

Hypophosphatemia is a common finding in renal transplant recipient. Phosphate-retention prior to transplant, re-distribution of phosphate from extracellular to intracellular compartment and restoration of normal homeostasis of phosphate imply that the body has adequate body store of phosphate in early post-transplant period. Hypophosphatemia in the early post transplant period tend to resolve spontaneously without complications. Prescription of oral phosphate supplement may slow down the recovery of residual hyperparathyroidism. Patients with isolated renal phosphate wasting after early transplant period would be expected to develop all the classical complications of hypophosphatemia, both acute and chronic, as their body store of phosphate may be depleted at any time. Definitive treatment of this group of patient is still lacking, but vitamin D analogues or possibly dipyridamole may help to correct the electrolyte disturbances. The time for starting treatment in this group of patients is uncertain as long as reliable markers of phosphate depletion remains undefined.

Table 1. The demographic data of patients (n=30)

	N
Age at the time of renal transplantation (years)	48 ± 2
Sex (M:F)	18 : 12
Living-related : cadaveric renal transplantation	1:29
Number of pre-emptive transplantation	5
Underlying renal disease	
Glomerulonephritis	10
Hypertension	9
Diabetes mellitus	6
Nephrolithiasis	1
Unknown	4
Duration of dialysis before transplantation (months)	21 ± 5
Duration of end-stage renal failure* (months)	22 ± 5

* Duration of end-stage renal failure is defined as the time starting from creatinine clearance less than 10ml/min/1.73m^2 to the time of renal transplantation.

Table 2: Factors associated with the development of post-transplantation hypophosphatemia

Pre-transplantaion parameter	Normophosphatemic patients (n=9)	Hypophosphatemic patients (n=21)	P value
Serum phosphate level (mmol/L)	1.39 ± 0.17	2.31 ± 0.09	<0.05
Serum calcium level (mmol/L)	2.26 ± 0.10	2.42 ± 0.04	NS
Serum alkaline phosphatase level (IU/L)	89 ± 13	89 ± 13	NS
PTH level (pmol/L)	42 ± 20	40 ± 12	NS
Duration of dialysis (week)	16 ± 10	24 ± 6	NS

Using non-paired Mann-Whitney test
N.B. the cumulative dose of steroid in both is not statistically different.

Table 3: Effect of oral phosphate supplement on the outcome of hypophosphatemic patients

	Group [H-PiS] (n=13)	Group [H-Pi] (n=8)
Time to recover from trough Pi (week)	6.6 ± 1.4	5.9 ± 1.4 [b]
Slope of PTH level vs time (mmol/L/week)	-0.42 ± 0.26	-0.42 ± 0.19[b]
Complication of hypophosphatemia	Nil	Nil

[b] P>0.05, using non-paired Mann-Whitney *U* test

Table 4 showed the influence of various factors on the action of Na/Pi co-transporters in renal proximal tubular cells

Stimulatory	***Inhibitory***
Phosphate-depleted diet [27-28]	Phosphate-enriched diet [27-28]
Insulin [24]	Parathyroid hormone [24]
Growth Hormone [24]	Parathyroid hormone-related protein [24]
Insuline-like growth factor I [24]	Transforming growth factors α and β [24]
Calcitriol [26]∗	Calcitonin [24]
Thyroid hormones [26]	Atrial natriuretic peptide [24]
All-trans-retinoic acid (atRA) [26]	Epidermal growth factor [24]
	Glucocorticoid [26]
	Estradiol (E2) [26]
	Soluble factor from TIO [25]

∗effects of calcitriol upon Na-Pi-cotransport have been demonstrated in the virtually only on vitamin D-depleted cells.

Figure 1. Distribution of first detectable trough phosphate level (t-trough) in 30 patients

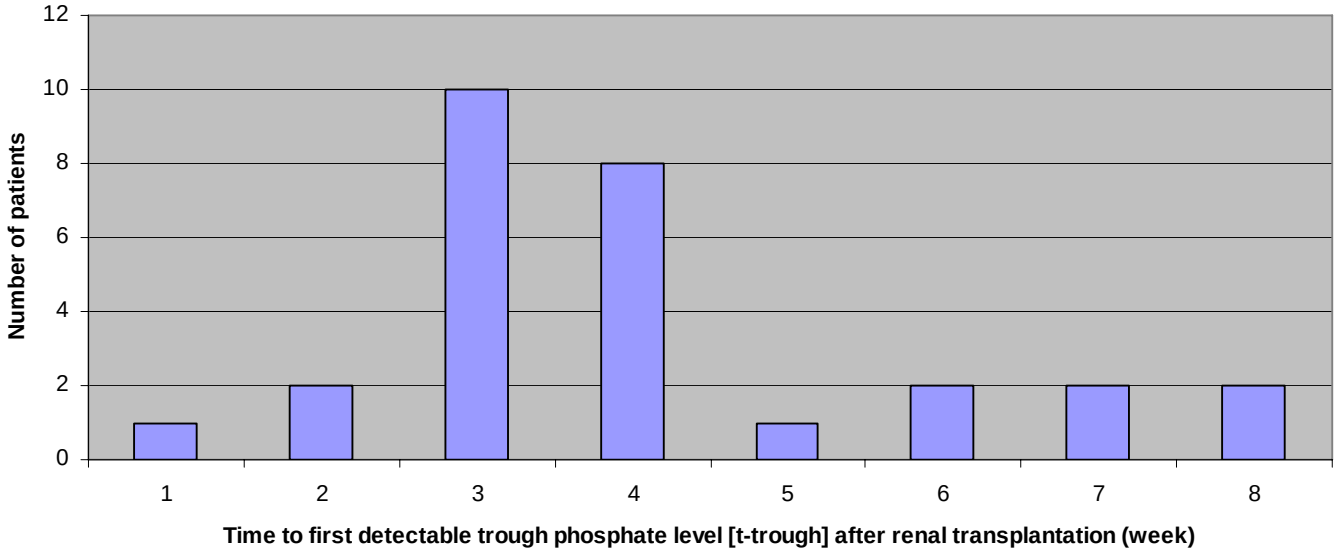
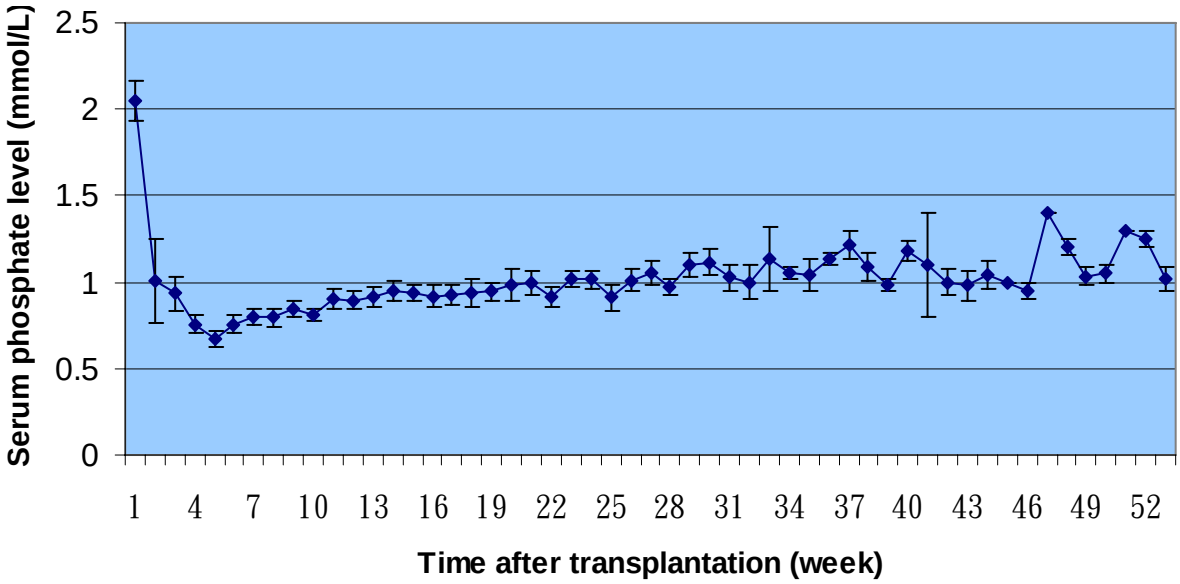
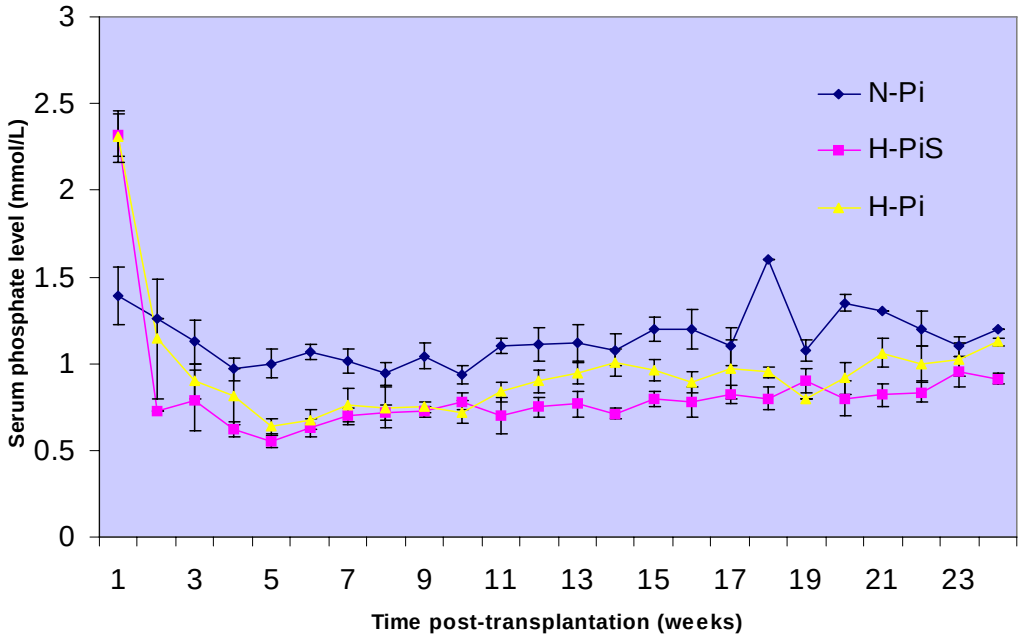


Figure 2: Serial serum phosphate level over the first twelve months after renal transplantation



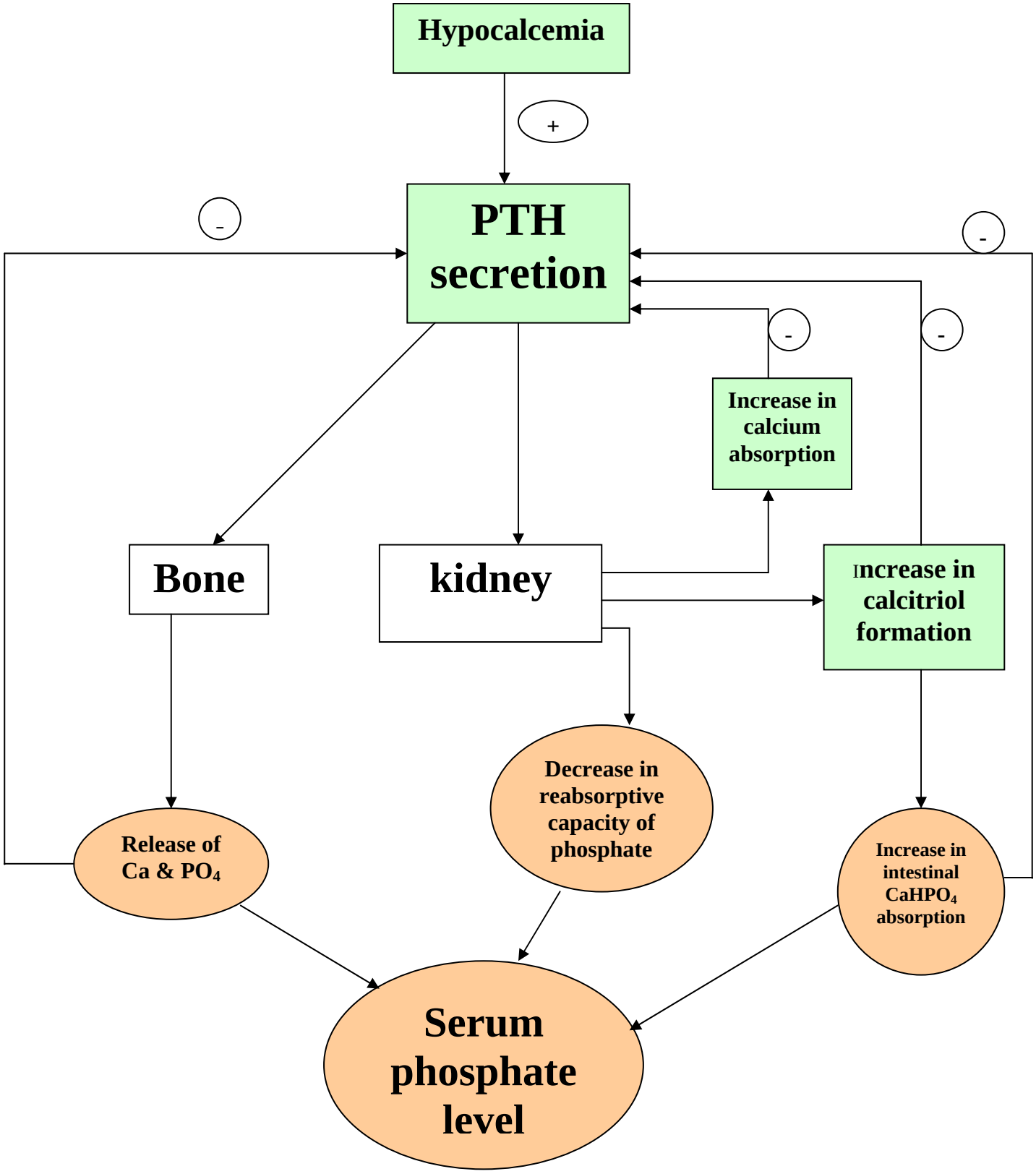
N.B. Serum Pi at time 0 was the mean serum phosphate concentration measured over 3 months prior to transplantation

Figure 3: Change in serum phosphate levels in three groups of patients with time post-transplantation



N.B. Serum Pi at time 0 was the mean serum phosphate concentration measured over 3 months prior to transplantation

Figure 4 shows the direct control of PTH on calcium homeostasis and the indirect effects on serum phosphate level



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