

## Biochemical Profile in Chronic Renal Failure\*

Ng Wai Yoong *BSc(Hons), PhD*, Lim See Heng, Tan It Koon *PhD, FACC, FRCPath*

Department of Pathology, SGH

### ABSTRACT

**Background.** The management of patients with chronic renal failure (CRF) requires close monitoring on a long-term basis. The purpose of this study was to examine the status of biochemical indicators used for assessment of renal, bone, liver and erythrocyte function or metabolism as well as for management of their respective dysfunction in patients requiring regular dialysis as outpatients.

**Methods.** A total of 1,327 consecutive patients (20–91 years; 681 males) attending outpatient centres for kidney dialysis over a 2-month period was studied. Serum concentrations of urea, creatinine, sodium, potassium, bicarbonate, calcium, phosphate, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), iron, total iron-binding capacity (TIBC), albumin, parathyroid hormone (PTH), ferritin, haemoglobin and glycated haemoglobin (HbA1c) were analysed.

**Results.** Parathyroid hormone (PTH) concentrations for the 1327 patients extended over a wide range (0.6–362 pmol/L) with elevated concentrations (>5.1 pmol/L, upper normal limit) observed in 80% of the patients. Increased phosphate (range 0.32–3.55 mmol/L) was found in 71% of patients. Calcium concentrations (1.33–3.55 mmol/L) were decreased in 1.1% and increased in 38% of patients. High ALP concentrations were found in 20% of patients. Significant correlation ( $p < 0.001$ ) was observed between urea and creatinine (Pearson coefficient  $r = 0.37$ ), between PTH and ALP ( $r = 0.57$ ), and between PTH and phosphate ( $r = 0.39$ ). There was no significant increase in ALT and AST concentrations, suggesting absence of hepatic injury. Low haemoglobin concentrations were noted in 85% of patients. Serum iron concentrations ranged from 3 to 50  $\mu\text{mol/L}$  with 26.7% having low iron status (serum iron  $< 11 \mu\text{mol/L}$ ). In contrast, high ferritin concentrations were found in 70% of patients. However, albumin and TIBC revealed suboptimal nutritional status in significant numbers of patients (58%  $< 37 \text{g/L}$ ; 87%  $< 44 \mu\text{mol/L}$  respectively).

**Conclusion.** High phosphate and PTH concentrations, anaemia and poor nutrition are problems faced by CRF patients on long-term regular dialysis. Slowing further progression to end-stage renal disease requires close attention to management practices although poor compliance with medical intervention and dietary advice may have contributed to the current status of biochemical profile.

*Keywords:* clinical chemistry, haemodialysis, kidney failure

### INTRODUCTION

According to the 2001 State of Health report, the incidence of patients on dialysis was 314 cases per million population in Singapore.<sup>1</sup> This increase from 203 cases per million population in 1999 or 55% in 2 years has been attributed to an increase in the ageing population (with 45.5% of new cases over 60 years of age) and in the incidence of diabetes and hypertension.

Both conditions are associated with progression of end-stage renal disease. Renal disease remains one of the top 10 leading causes of death since the 1960s.

Chronic renal failure could be due to primary kidney disease, such as glomerulonephritis and renal artery stenosis, diabetes or hypertension. A result of metabolic and haemodynamic factors and if left untreated, kidney function will further deteriorate as indicated by a fall in glomerular filtration rate. Eventually, end-stage renal disease sets in. In the individual burdened with impaired kidney function,

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Table 1. Summary of analytes concentrations obtained from the chronic renal failure patients.

	Concentration*	Range	Reference Interval
Urea	22.8±4.8	5.9–43.3	2.8–7.7mmol/L
Creatinine	894±178	345–1582	44 – 141µmol/L
Sodium	137	125–149	135 - 145mmol/L
Potassium	4.7	3.1–7.2	3.3–4.9mmol/L
Bicarbonate	19.3±2.28	9.0–33.0	19.0–31.0mmol/L
Calcium	2.53	1.33–3.55	2.10–2.60mmol/L
Adjusted calcium	2.59	1.53–3.63	–
Phosphate	1.65	0.32–3.55	0.77–1.38mmol/L
ALP	73	20–702	32–103U/L
ALT	16	6–275	7–36U/L
AST	16	6–82	15–33U/L
Iron	13	3–50	11–29µmol/L
TIBC	36	9–72	44–73µmol/L
Albumin	36	20–45	37–51g/L
PTH	14.7	0.60–362	0.5–5.1pmol/L
Ferritin	450	8–2799	32–294µg/L
Haemoglobin	10.6	5.1–18.3	12.0–18.0g/dL
HbA1c	7.1±1.6	4.2–13.7	4.6–6.4%
TIBC saturation	37	9–100	20–50%

\* mean±SD given for normally distributed levels, otherwise median values are depicted.

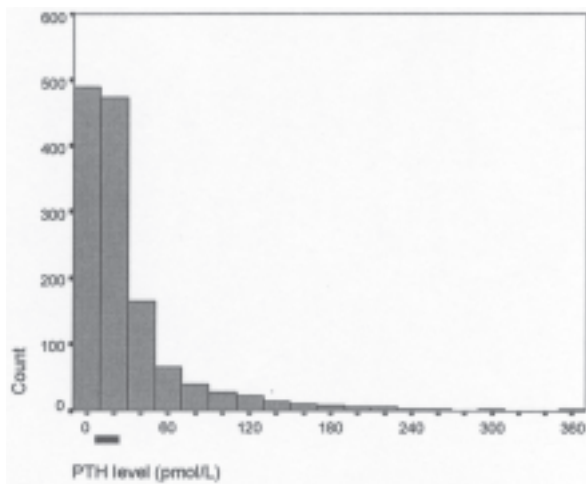
progressive renal failure gives rise to a steady increase in parathyroid hormone (PTH) concentrations as a result of 2 stimuli — reduced renal clearance of phosphate and reduced renal secretion of calcitriol, both of which cause decreased serum calcium concentrations. After years of chronic renal failure (CRF), secondary hyperparathyroidism would cause increase in bone turnover, leading to elevated serum alkaline phosphatase (ALP) concentrations (due to isoenzymes from the osteoblasts).<sup>2,3</sup> In addition, the failing kidney is also unable to produce vital hormones for red cell synthesis. Reduced erythropoietin production is primarily the reason for the anaemia seen in the disease. There is associated cardiovascular risk with anaemia and to correct it, blood transfusions and/or recombinant human erythropoietin are administered.<sup>4,5</sup>

Biochemical indicators are routinely monitored to enable timely assessment of strategies and management programmes in patient care. For example, determinations of urea and creatinine concentrations are necessary to confirm the effectiveness of dialysis and the measurements of iron and ferritin are required to assess the presence of iron deficiency or overload and monitor the effectiveness of therapy.

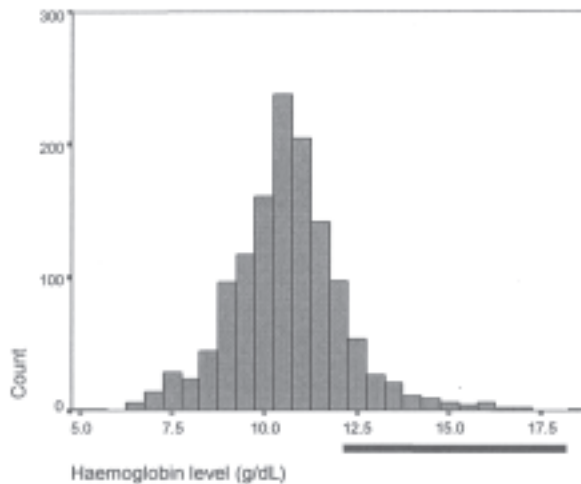
In this study, we examined the status of 18 biochemical indicators for renal, bone, liver and erythrocyte function or metabolism in CRF in a population receiving twice monthly haemodialysis as outpatients. An overview of the biochemical profiles for the patients can assist the clinician in making adjustments to clinical management practices.

## METHODS

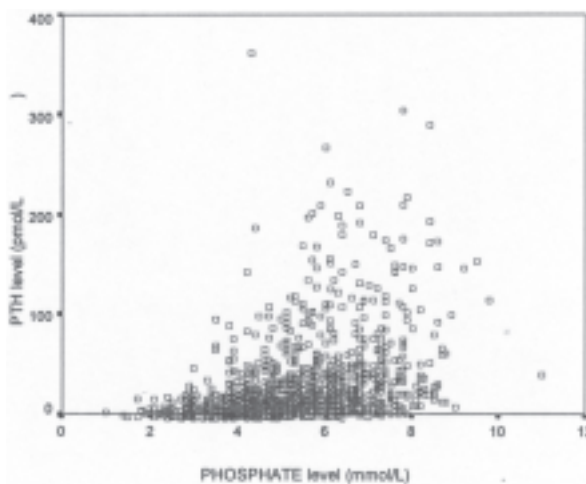
All patients had been undergoing treatment with haemodialysis for at least 2 months. Biochemical tests were performed on a total of 1,327 CRF patients (681 males and 646 females) with mean age of 53.9 years (range 20–91 years). Blood collection was made prior to dialysis. Serum concentrations of urea, creatinine, sodium, potassium, bicarbonate, calcium, phosphate, ALP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), iron, total iron-binding capacity (TIBC) and albumin were measured on the Roche/Hitachi *MODULAR* analyser. PTH and ferritin were measured on Roche Elecsys 2010 and glycosylated haemoglobin (HbA1c) on the Bio-Rad Variant II system. Haemoglobin concentrations were measured on the Beckman-Coulter HmX. TIBC saturation was determined by the percentage of iron concentrations over TIBC concentrations.



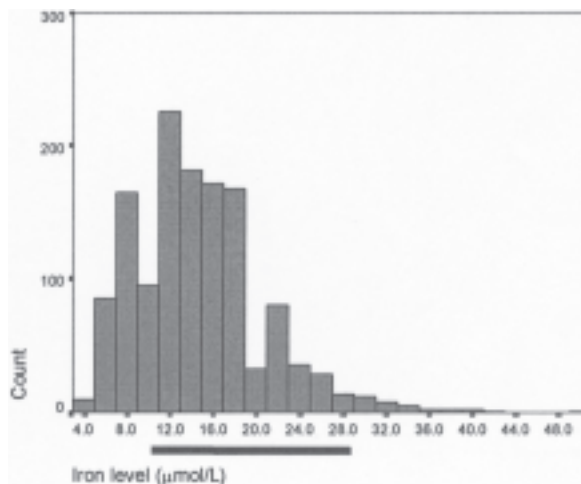
(a) Distribution of PTH



(a) Haemoglobin



(b) Relationship between PTH and phosphate in CRF



(b) Iron

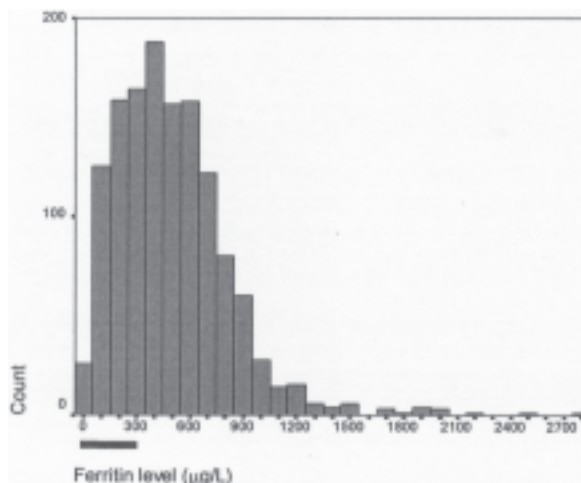
Fig. 1. Serum PTH and phosphate in CRF patients (bar depicts reference interval).

**Statistical Analyses**

All analyses were performed using SPSS 10.0 for Windows. Associations between continuous variables are provided by the Pearson's coefficient of correlation. Where serum concentrations are not distributed normally as determined by the Kolmogorov-Smirnov statistic, median levels are given instead of the mean and standard deviation.

**RESULTS**

A significant association between serum urea and creatinine was observed, as expected ( $r=0.37$ ,  $p<0.001$ ). Hyponatraemia ( $<135\text{mmol/L}$ ) was noted in 19%, hyperkalaemia ( $>5.0\text{mmol/L}$ ) in 39% and acidosis (bicarbonate  $<19.0\text{mmol/L}$ ) in 44% of patients (Table 1). In this haemodialysis population,



(c) Ferritin

Fig. 2. Iron status markers (bar depicts reference interval).

more than a quarter were suffering from diabetes mellitus based on the 28.3% requiring HbA1c measurements. According to clinical guidelines issued by the Ministry of Health, glycaemic control were unacceptable (HbA1c>8.0%) in 28%, suboptimal (7.1–8.0%) in 16% and optimal (6.5–7.0%) in only 15% of the diabetes patients.<sup>6</sup>

Phosphate concentrations were high in 71% of patients and a correlation with creatinine was observed ( $r=0.26$ ,  $p<0.001$ ) indicating that the magnitude of hyperphosphataemia was related to the severity of renal impairment. Raised PTH levels ( $>5.1\text{pmol/L}$ ) were found in about 80% of the cohort (Fig. 1a). PTH concentrations extended over a wide range, from 0.6 to 362pmol/L and were significantly correlated with ALP ( $r=0.57$ ,  $p<0.001$ ) and phosphate concentrations ( $r=0.39$ ,  $p<0.001$ ) (Fig. 1b). Only 1.1% had reduced calcium but increased concentrations were found in 38% of patients. Calcium concentrations corrected for serum albumin concentrations were similar to unadjusted levels (Table 1). Elevated serum ALP activity unassociated with increased concentrations of liver enzymes ALT and AST was observed in at least 20% of patients, indicating the presence of renal osteodystrophy.

ALT and AST concentrations were increased in only small numbers of patients (7.2% and 4.4% respectively) indicating low occurrence of acute hepatic damage.

Eighty-five percent of patients had low haemoglobin concentrations ( $<12\text{g/dL}$ ) (Fig. 2a). Low iron status ( $<11.0\mu\text{mol/L}$ ) was found in 28.0% of these patients (Fig. 2b). In contrast, 70% of the CRF patients had high ferritin concentrations (Fig. 2c). Ninety-eight percent of the cohort had TIBC saturation concentrations greater than 20%.

Analysis of albumin and TIBC concentrations also revealed that 58% had  $<37\text{g/L}$  albumin while 87% had  $<44\mu\text{mol/L}$  TIBC, indicating possibly suboptimal nutritional status in significant numbers of patients.

## DISCUSSION

Using a criterion of PTH  $>26.5\text{pmol/L}$  (or  $250\text{pg/mL}$ ) as an indicator for the presence of hyperparathyroidism, 30% of this cohort developed secondary hyperparathyroidism.<sup>7</sup> Retention of serum phosphate levels leading to secondary hyperparathyroidism is reflected by the significant correlation between PTH and phosphate concentrations. Good correlation between PTH and ALP concentrations suggests that bone remodelling

activity is influenced by PTH levels. Although chronic renal failure and increase in serum phosphate are expected to give rise to hypocalcaemia, it is noted that only 1.1% of patients had low serum calcium concentrations. Although ionised calcium concentrations were not available, calcium levels corrected for serum albumin were similar to unadjusted levels (median  $2.59\text{mmol/L}$  cf. unadjusted  $2.53\text{mmol/L}$ ). In the cohort, only 38% had raised calcium concentrations. This is perhaps an indication of some tertiary hyperparathyroidism, where despite normal or elevated calcium levels, PTH concentrations remained high. Calcium-based phosphate-binders (calcium carbonate, calcium acetate) given to control high phosphate levels could also have contributed to the serum calcium concentrations.

Seventy-one percent of patients had phosphate exceeding  $1.38\text{mmol/L}$ , the upper limit of reference interval. Using a criterion of  $>1.77\text{mmol/L}$  as indication of hyperphosphataemia, 41.5% were found to have hyperphosphataemia.<sup>8</sup> In comparison, a multi-centre study in Italy and a separate study in America reported the presence of hyperphosphataemia in 51% and  $>60\%$  of patients, respectively.<sup>9</sup> To minimise bone disease, management strategies require control of phosphate and PTH concentrations. Although clinical modalities and treatment regimes are unavailable for this study, phosphate-binders to reduce serum phosphate and vitamin D analogs to suppress hyperparathyroidism are established protocols. Those who do not respond to such treatment may require surgical removal of the parathyroid.<sup>10,11</sup>

In this cohort of 1327 patients, 85% had Hb  $<12.0\text{g/dL}$  and 67% with  $<10.0\text{g/dL}$  Hb. In the United Kingdom, the national Renal Association's target of Hb  $>10.0\text{g/dL}$  has been advocated for the management of anaemia, a desired goal also mirrored ( $11\text{--}12\text{g/dL}$ ) by the European authorities.<sup>12-14</sup> When iron stores are present, but cannot be mobilised rapidly enough to maintain maximal erythropoietin induced erythropoiesis, a state of functional iron deficiency is said to occur. Ferritin from tissues gives a measure of iron stores. While low circulating levels give good indication of a deficient state, elevated levels may mean tissue injury, particularly in the liver; malignancies or concurrent inflammation present. Absolute iron deficiency has been defined as a transferrin saturation  $<20\%$  and ferritin  $<100\mu\text{g/L}$ .<sup>15,16</sup>

An indirect measure of transferrin saturation is provided by TIBC saturation. As indicated by TIBC saturation  $>20\%$ , the majority of patients (98%) in this study has no functional iron deficiency. It is cognizant

that blood collection times may vary amongst the dialysis centres. The known diurnal variation of iron, being highest in the morning, may have had an effect on the iron profile seen in this study. In this study, controlled protein intake (a common dietary recommendation to renal patients) may have contributed to hypoalbuminaemia in 58% and low concentrations of TIBC in 87% of patients. It should also be noted that low concentrations of serum albumin may also be due to hydration status, malabsorption, inflammation and acute liver disorders.

## CONCLUSION

The significant proportion of patients with hyponatraemia (19%), hyperkalaemia (40%) and acidosis (44%) confirms the importance of regular monitoring of electrolyte concentrations in the management of CRF patients. High phosphate concentrations, anaemia and poor nutrition are also problems faced by CRF patients on dialysis. To impede progression to end-stage renal disease, close attention to management practices and compliance with medical intervention and dietary advice is necessary to improve the quality of life and prolong the life span of patients.

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