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Neuro-Fuzzy Technology as a Predictor of Parathyroid Hormone Level in Hemodialysis Patients

Chiou-An Chen,[1,5] Yu-Chuan Li,[2] Yuh-Feng Lin,[1] Fu-Chiu Yu,[1]
Wei-Hsin Huang[3] and Jainn-Shiun Chiu[4]

[1]Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan
[2]Institute of Biomedical Informatics, National Yang Ming University, Taipei, Taiwan
[3]Division of Nephrology, Department of Internal Medicine, Taitung Hospital, Taitung, Taiwan
[4]Department of Nuclear Medicine, Buddhist Dalin Tzu Chi General Hospital, Chiayi and Department of Medicine, College of Medicine, Tzu Chi University, Hualien, Taiwan
[5]Graduate Institute of Medical Informatics, Taipei Medical University, Taipei, Taiwan

Chen, C.-A., Li, Y.-C., Lin, Y.-F., Yu, F.-C., Huang, W.-H. and Chiu, J.-S. *Neuro-Fuzzy Technology as a Predictor of Parathyroid Hormone Level in Hemodialysis Patients*. Tohoku J. Exp. Med., 2007, **211** (1), 81-87 —— Measuring the plasma parathyroid hormone (PTH) concentration is crucial to evaluate renal bone disease in patients with renal failure. Although frequent measurement is needed to avoid inadequate prescription of phosphate binders and vitamin D preparations, artificial intelligence can repeatedly perform the forecasting tasks and may be a satisfactory substitute for laboratory tests. Neuro-fuzzy technology represents a promising forecasting application in clinical medicine. We therefore constructed a coactive neuro-fuzzy inference system (CANFIS) to predict plasma PTH concentrations in hemodialysis patients. The CANFIS was constructed with clinical parameters (patient age, plasma albumin, calcium, phosphorus, alkaline phosphatase, and calcium-phosphorus product) from a cohort of hemodialysis patients, and plasma PTH concentration measured by radioimmunoassay (RIA) was the supervised outcome. The accuracy of the CANFIS was prospectively compared with RIA in another hospital. Plasma PTH concentrations measured by RIA and predicted by CANFIS were 179.04 ± 38.18 ng/l and 179.34 ± 37.76 ng/l, respectively ($p = 0.15$). The CANFIS was able to precisely estimate plasma PTH concentrations in hemodialysis patients. These results suggest that the neuro-fuzzy technology, based on limited clinical parameters, is an excellent alternative to RIA for accurately predicting plasma PTH concentration in hemodialysis patients.
———— fuzzy logic; neural network; parathyroid hormone; hemodialysis

Renal bone disease is an important cause of morbidity in hemodialysis patients. It is usually stratified as high turnover bone disease (osteitis fibrosa cystica) or low turnover bone disease (osteomalacia and adynamic bone disease), based on plasma concentration of parathyroid hormone (PTH) and characteristic findings of bone histomorphometry. Because bone biopsy is an invasive procedure, determination of plasma PTH concentration is fundamental for optimal inter-

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Correspondence: Jainn-Shiun Chiu, M.D., Department of Nuclear Medicine, Buddhist Dalin Tzu Chi General Hospital, No. 2, Minsheng Rd., Dalin Township, Chiayi County 622, Taiwan.
e-mail: shiunkle@mail2000.com.tw

vention. Generally, dosages of phosphate binders, vitamin D analogues, or calcimimetic drugs are based on plasma calcium, inorganic phosphorus, and especially PTH levels (Elder 2002). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) *Clinical Practice Guidelines for Bone Metabolism and Disease* suggests monitoring plasma PTH levels every 3 months for dialysis patients (National Kidney Foundation 2003). In practice, however, many dialysis institutions routinely monitor plasma PTH concentrations for dialysis patients at intervals of every six months or longer.

In addition to the increased prevalence of low turnover bone disease in uremic patients, overzealous empirical treatment with vitamin D analogues could result in the occurrence of low turnover bone disease. Therefore, it is necessary to frequently monitor plasma PTH concentration by K/DOQI-recommended radioimmunoassay (RIA) intervals. With a goal of guaranteeing dialytic quality without increasing the cost of frequent measurement, we postulated that a predictive model using artificial intelligence software can repeatedly perform the forecasting tasks and may be a satisfactory substitute for measuring PTH by RIA. Therefore, we constructed a coactive neuro-fuzzy inference system (CANFIS) (Hardalac et al. 2004), which is an advanced combination technology of fuzzy logic and neural network to investigate the feasibility of quantitatively predicting plasma PTH concentration for hemodialysis patients.

Methods

Patients enrolled in the study were 121 stable hemodialysis patients from an independent dialysis unit of Buddhist Dalin Tzu Chi General Hospital, Chiayi County, a teaching hospital in western Taiwan. These patients served as the training group (Unit A). In addition, 32 stable hemodialysis patients from an independent dialysis unit of Taitung Hospital, Taitung City, a general hospital in eastern Taiwan were enrolled as the test group (Unit B). All patients were treated on maintenance hemodialysis for more than six months without any concurrently acute illness at the time of enrollment. The Institutional Review Board Ethics Committee on Human Studies of Buddhist Dalin Tzu Chi General Hospital approved the multi-institutions study. Informed consent for enrolled patients was not required for clinical data collection from medical records according to the protocol of our institutional review board. To preserve patient confidentiality, direct patient identifiers were not collected. Data were reported only in aggregate form.

For the quantitative prediction of plasma PTH concentration, we used the software NeuroSolutions 4.32 (NeuroDimension, Inc., Gainesville, FL, USA) to construct a CANFIS network using a training set of patients from dialysis unit A. To choose adequate predictors typically available to physicians, we selected the most relevant parameters including age of patient, plasma albumin, calcium, phosphorus, alkaline phosphatase, and calcium-phosphorus product, which were routinely monitored every month in the dialysis unit, as input variables. Plasma PTH concentration measured by RIA at dialysis unit A (PTH-RIA_A) was entered as the output variable. In dialysis unit A, blood albumin, calcium, phosphorus, and alkaline phosphatase concentrations were measured by an automatic biochemistry analyzer (Hitachi 7170; Hitachi Co., Tokyo) and plasma PTH concentration was measured by RIA (Active I-PTH DSL-8000; Diagnostic Systems Laboratories, Inc., Webster, TX, USA). All input and output variables were collected simultaneously.

Before training the CANFIS, we randomly selected 30 patients (25%) from 121 patients as typical examples for cross validation that monitors the error on an independent set of data and stops training when the error begins to increase. All six input variables were used as inputs and PTH-RIA_A was used as the supervised output to construct the CNAFIS network. In selection of membership function and fuzzy model, we used three bell-shaped curves for each input and the Takagi-Sugeno-Kang fuzzy model, respectively. With the help of batch learning, the axon was chosen as the transfer function to store input. The step size and momentum coefficient of the learning rule were set as 1.00 and 0.70, respectively. The CANFIS network was trained after several iterations by using mean square error to terminate the supervised learning.

After prospectively collecting the input variables from dialysis unit B in the same manner as from dialysis unit A, the CANFIS was tested in the external validation group while the CANFIS was blinded to the actual outcome. Plasma PTH concentration for each patient predicted by CANFIS (PTH-CANFIS) was compared with the actual PTH measurement at dialysis unit B (PTH-RIA_B). In dialysis unit B, blood albumin, calcium, phosphorus, and alkaline phosphatase concentrations were

measured by an automatic biochemistry analyzer (Olympus AU400, Olympus Co., Tokyo) and plasma PTH concentration was measured by RIA (Allegro, Nichols Institute, San Juan Capistrano, CA, USA). As in Unit A, the input and output variables were collected simultaneously.

Data were analyzed using the MedCalc 8.1 (MedCalc Software Inc., Mariakerke, Belgium) and expressed as the mean ± standard error or as a ratio. The Mann-Whitney's U-test or Chi-square test was used to compare patient characteristics between training and external validation groups. The PTH-RIA_B and PTH-CANFIS were compared by the Wilcoxon test. Spearman's coefficient of rank correlation and Passing-Bablok regression (Passing and Bablok 1983) were adapted to evaluate the performance of the CANFIS in predicting the plasma PTH concentration for hemodialysis patients. High correlation means that the measurements by the two methods are linearly related. However, this high correlation does not mean that the two methods agree. To evaluate the interchangeability of two methods, the Passing-Bablok regression describes a linear regression procedure with no special assumptions regarding the distribution of the samples and the measurement errors. The result does not depend on the assignment of the methods to variables. The slope and intercept are calculated with their 95% confidence intervals. These confidence intervals are used to determine whether there is only a chance difference between slope and one and between intercept and zero.

Results

The results of patient characteristics for the two dialysis units are shown in Table 1. No statistical differences were found between the training (dialysis unit A) and external validation (dialysis unit B) groups except plasma calcium concentration. After the training process for the CANFIS, total epochs were 911 iterations. The PTH-RIA_B (179.04 ± 38.18 ng/l) and PTH-CANFIS (179.34 ± 37.76 ng/l) were not statisti-

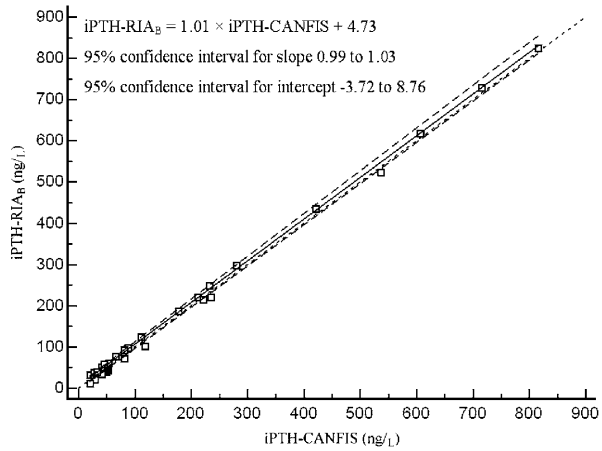

Fig. 1. Passing-Bablok regression analysis. The Plasma PTH concentration predicted by the CANFIS is plotted against the results of the radioimmunometric assay that shows a scatter diagram with regression line (solid line), the 95% confidence interval for the regression line (dashed lines), and identity line (X = Y, dotted line). The results indicate that both methods are interchangeable without statistically significant deviation ($p > 0.10$).

Table 1. Patient characteristics of two dialysis units.

	Dialysis unit A (n = 121)	Dialysis unit B (n = 32)	p value
Male/Female	58/63	15/17	0.93
Age (years)	59.98 ± 1.19	62.53 ± 2.19	0.25
Albumin (g/l)	39.12 ± 0.33	39.66 ± 1.19	0.13
Alkaline phosphatase (U/l)	133.31 ± 4.92	174.31 ± 34.22	0.66
Calcium (mmol/l)	2.33 ± 0.02	2.42 ± 0.04	0.03
Phosphorus (mmol/l)	1.40 ± 0.04	1.42 ± 0.08	0.67
Calcium-phosphorus product	3.26 ± 0.10	3.44 ± 0.21	0.35
Parathyroid hormone (ng/l)	126.57 ± 14.36	179.04 ± 38.18	0.11

The p values were derived from Mann-Whitney's U-test for continuous variables and Chi-square test for categorical variable.

cally different ($p = 0.15$). Spearman's coefficient of rank correlation between PTH-RIA_B and PTH-CANFIS was 0.98 ($p < 0.001$). The relationship between PTH-RIA_B and PTH-CANFIS by the Passing-Bablok regression (Fig. 1) was PTH-RIA_B = 1.01 × PTH-CANFIS + 4.73, with a 95% confidence interval for slope 0.99 to 1.03 which includes one and for intercept –3.72 to 8.76 which includes zero, indicating that both methods are interchangeable without statistically significant deviation ($p > 0.10$).

Discussion

PTH plays a central role in the pathogenesis of renal bone disease. Hyperparathyroidism is also associated with an increase in the relative risk of death, cardiovascular, and fracture-related hospitalization in hemodialysis patients (Block et al. 2004). Hence, we suggest that frequently monitoring plasma PTH concentration in hemodialysis patient should be carried out in spite of increased costs. Although there are advancements in hemodialysis care in Taiwan, the interval for PTH measurement in most dialysis centers is every six months or longer. In research not previously reported, our goal was to develop a neuro-fuzzy technology as an alternative to RIA measurement to predict PTH levels in hemodialysis patients, and prospectively verify the usefulness of this technology in a different group. With the help of Passing-Bablok regression, which describes statistics without special assumptions about the distribution of the samples and measurement errors, we successfully displayed the interchangeability between the CANFIS and RIA.

Neuro-fuzzy technology is increasingly used for data analysis and decision-making purposes in clinical medicine (Hanai and Honda 2004; Ramesh et al. 2004). Recently, this technology has been used for accurately predicting renal function from serum creatinine (Marshall et al. 2005). Although the regulation of PTH in dialysis patients is complicated, a CANFIS can achieve a good prediction by using a fuzzy inference system as a preprocessor in a neural network to optimize fuzzy parameters of membership function with backpropagation. This fuzzification makes the neural network's task easier by characterizing inputs that are not easily discretized. Therefore, neuro-fuzzy technology combines the benefits of neural networks and fuzzy inference systems and enables us to obtain better results. Furthermore, the neuro-fuzzy approach can make use of combinations of categorical and continuous variables. No assumptions of variable distribution and interdependence are necessary. The performance of neuro-fuzzy technology will continuously improve over time because neuro-fuzzy technology can be constantly retrained as more cases accumulate. Since a CANFIS possesses these advantages, it is more computationally intensive than other artificial intelligent models. To obtain higher accuracy within a fixed amount of computational time, the flexible membership function and adaptive learning procedure may be further investigated.

In particular, we used limited clinical variables for constructing a workable neuro-fuzzy technology. Neuro-fuzzy technology itself can deal with more input variables in predictive task and prune insignificant variables during the training process. However, we selected only six variables that are usually measured in hemodialysis patients. Our reason is that for any forecasting model to be useful in making clinical decisions, it should use only parameters that are readily available to the clinician at the time of triage (Chiu et al. 2005). This is an essential issue since fewer inputs may simplify the process for clinicians in determining subsequent decisions rapidly (Bates et al. 2003). On this basis the input variables we chose in this study not only contained the characteristic of routine measurement in monthly dialytic workflow, but also possessed the individually physiologic meanings. Age, which is determined from basic demographic data in the medical record, can be easily calculated. In one study conducted by Mehrotra and colleagues (Mehrotra et al. 2004), the results showed that increasing age is inversely correlated with PTH in hemodialysis patients. The diminished reactiveness of parathyroid glands is perhaps related to age-dependent accumulation of uremic toxins in elderly hemodialysis patients. In addition, nutrition has been

proposed to be involved as an additional factor in the expression of renal bone disease. A higher PTH concentration has been associated with a normal albumin level in hemodialysis patients, implicating a better visceral and somatic protein status (Avram et al. 1996). On the other hand, the nonlinear phenomenon of biological nature is recognized in medical investigations. By virtue of inherent benefits of the neuro-fuzzy technique with built-in nonlinear functions, the linear adjustment between measured calcium concentration and albumin level can be avoided (Payne et al. 1973). Taken together, low albumin level and increasing age reduce PTH secretion and are important factors of functional status of the parathyroid glands during maintenance dialysis (Heaf and Lokkegard 1998). Hence, patient age and albumin level should be considered as part of the inputs in the neuro-fuzzy model.

Since the kidney plays a significant role in mineral homeostasis by preserving external balance for calcium and phosphorus, the occurrence of metabolic bone disease in patients with renal failure is expected. Persistent phosphorus retention, together with a reciprocal fall in the concentration of extracellular calcium, is associated with prolonged stimulation of PTH synthesis and secretion from the parathyroid glands in renal failure. Decreased phosphorus excretion also reduces the levels of calcitriol, which may result in malabsorption of calcium, and further stimulation of PTH secretion. These continuously vicious effects may lead to nodular hyperplasia of the parathyroid glands with underexpression of the calcium-sensing receptor and the vitamin D receptor. These hyperparathyroid cells lose critical components of the system to mount a proper reaction for elevated circumfused calcium concentration and/or suppressive input of calcitriol. The resulting secondary hyperparathyroidism, a main driver of renal bone disease, is in turn associated with vascular and other soft tissue calcification (Cunningham 2004). In addition, the kidney is the major organ accounting for the excretion of $\beta 2$-microglobulin and aluminum, substances involved in the induction of dialysis-related amyloidosis and osteomalacia, respectively. On the other hand, elevated levels of the calcium-phosphorus product play a pivotal role in vascular calcification, calciphylaxis, and cardiovascular morbidity and mortality. A lowering of levels such that the calcium-phosphorus product is below 55 mg^2/dl^2 might well be one of the therapeutic management strategies in patients with renal failure (Levin and Hoenich 2001). Therefore, assembling calcium, phosphorus, and calcium-phosphorus product provides an adequate merging utilization of input variables in building the model.

Alkaline phosphatase, a glycosylated protein produced by at least five different organs, is one of the most widely used noninvasive tests for clinical diagnosis of renal bone disease. The level of alkaline phosphatase is suggestive of discrimination between hyperparathyroid bone disease and adynamic bone disease even though the measurement of alkaline phosphatase is short of specificity for skeletal disease (Roe and Cassidy 2000). Bone-specific alkaline phosphatase can be utilized as a biochemical marker of bone formation to enhance the discriminatory ability among various subtypes of renal bone disease. However, the measurement of bone-specific alkaline phosphatase is time-consuming and needs exhausting techniques to improve the sensitivity of this maker (Ferreira and Drueke 2000). There are also insufficient evidence-based reports available to recommend the routine measurement of bone-specific alkaline phosphatase (Martin et al. 2004). Therefore, bone-specific alkaline phosphatase is not ordinarily used as widely as alkaline phosphatase in every dialysis unit. Correspondingly, a number of biochemical markers involving bone formation and resorption are increasingly evaluated in the diagnosis and monitoring of renal bone disease including osteocalcin, pyridinoline, tartrate-resistant acid phosphatase isoenzyme 5b, and osteoprotegerin etc (Ferreira 2000). These biochemical markers might be encouragingly practical in the future but they are not currently easily achieved at the point of care, which may influence the model's applicability and generalization. Therefore, these laboratory-based biomarkers are not appropriate for selection as our

neuro-fuzzy inputs.

To avoid the complexity of a model, it is not necessary to add other variables such as patient's medications or dialytic prescriptions even though they are known to have a significant impact on PTH levels. Several reports of the application of artificial intelligence in medicine indicate an excellent fit of the model to a given set of data (Rae et al. 1999; Oates et al. 2005). Results that were too imposing usually were derived from overfitted models, where too many parameters were enrolled. The challenge is to train a network to recognize patterns without overfitting, thus avoiding model complexity for physicians. We decided to use cross-section biochemical data as our input variables since we seldom use time-series data in daily practice. When the cross-section method could not provide proper analysis or explain underlying phenomenon in nature, the application of a time-series method is considered to discover the latent pattern in the mining dataset that has the characteristic of time sequence. In our study, we appropriately demonstrated that using neuro-fuzzy technology with fewer, but important cross-section variables, to forecast PTH levels in hemodialysis patients is feasible. Nevertheless, we will try to design a future study using a time-series database to investigate the influence of a longitudinal dataset.

Facing rapid developments of information technology in clinical medicine, some physicians might hesitate to use this evolving application of a neuro-fuzzy system. In fact, much artificial intelligence creation software also offers a function to package the trained neuro-fuzzy system into an executable file, and make it available on the Internet for anyone to download. Our future study will focus on prospective multi-center implementations of a web-based platform using neuro-fuzzy technology as the kernel engine for clinicians to do an online prediction of the PTH level in hemodialysis patients.

In conclusion, this study supports neuro-fuzzy technology for the prediction of plasma PTH concentration in hemodialysis patients as a useful tool that shows accuracy in different dialysis units. Furthermore, we hope that artificial intelligence may encourage clinical nephrologists to monitor PTH levels more frequently and lessen the impact of renal bone disease for hemodialysis patients in the future.

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