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Parathyroid Hormone in Kidney Failure

Volume Editor
Morrell M. Avram, Brooklyn, N.Y.

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Parathyroid Hormone in Kidney Failure

Edited by
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Contributions to Nephrology

Vol. 20

S. Karger · Basel · München · Paris · London · New York · Sydney

Morrell Michael Avram, BS, MD, FACP

Dedication

This volume derives from a career-long interest in understanding why patients with renal diseases develop clinical illness. As a teacher and clinical researcher, I have had the opportunity of learning from fellows, junior faculty and medical students. Few fields of medicine have evolved so rapidly as nephrology in which uremia changed from a universally fatal disease to a manageable and treatable morbid complication. It is this treatment necessity which now attracts my full-time energies. Because I believe that parathyroid hormone contributes to sickness in my patients, both an investigative interest and the current conference resulted.

My own career parallels, since 1959, the expansion and indeed explosion of informative generation and exchange in nephrology. I anticipate that the decade of the 1980s, which we have entered, will witness a further experimental growth of our knowledge to detect and treat renal disorders by altering the immune response, use of bionic devices and by prevention of genetic and acquired renal diseases.

It is toward this end that this conference, held at the The Long Island College Hospital in which I spend the majority of my waking hours, was poised to inaugurate the 1980s.

Loving thanks are due my wife, Maria, and my children, Rella, Marc, Eric, Mathew and David for putting up with the rigors and excrescences of a medical practice, academia and clinical research. I want to reaffirm my love for Brooklyn Heights and the City of New York for providing an exciting and productive medical home.

Morrell M. Avram, MD
Brooklyn, N.Y.
May 1980

Acknowledgement

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About the Editor

Morrell Michael Avram, BS, MD, FACP served his internship, residency and renal fellowship at The Long Island College Hospital, where he was appointed the first Chief of Nephrology in 1970. From that time on, supported by competitive grant awards from the New York State Research Council through its Kidney Disease Institute, The New York Kidney Foundation, The Artificial Kidney Foundation and others, his program has undergone continuous expansion in scope and service.

No less than 41 fellows, some now division chiefs in their own right throughout the United States, and a score of junior associates have trained under Dr. *Avram.* Graduates of his program are furthering nephrology practice and research throughout the world. He has served on the faculty of Downstate Medical Center since 1963 where he was recently promoted to the rank of Professor of Medicine.

Maintaining a continuing interest in the abnormal metabolism of uremia, Dr. *Avram* has published 42 papers preceding this volume. These papers concern the genesis of intoxication in uremia with a progressive indictment of parathyroid hormone. Dr. *Avram* was the first to demonstrate the feasibility of life prolongation in diabetics by hemodialysis, noted the high incidence of chronic pancreatitis in uremia, reported the impact of taste alterations in renal disease and described the concept of medical nephrectomy using mercurial salts.

Dr. *Avram* has been a leader in organizational nephrology having held numerous elected posts including President of the New York Society of Nephrology and the New York Regional Renal Disease Network. He is the founder of the Nephrology foundation of Brooklyn. He is a sought after teacher who lectures internationally while devoting time to electives for senior medical students.

A staunch Brooklyn booster, Dr. *Avram* lives in Brooklyn Heights with his wife and five children in a traditional, but updated, brownstone house.

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Introduction (Symposium Overview)

Deranged calcium metabolism was one of the early chemical abnormalities identified in uremia. Association of the parathyroid gland with bone demineralization and pathological fractures followed the nearly constant finding of quadriglandular hyperplasia in patients dying after protracted renal failure. Once technical advances in radioimmunoassay of peptide hormones simplified measurement of parathyroid hormone (PTH) the extraordinarily high levels present in secondary hyperparathyroidism were appreciated. Evidence that excessive PTH might be responsible for more than bone injury in uremia has been accumulating to the point where *Massry* (1) and *Avram et al.* (2, 3) hypothesized that PTH might be a major multisystem toxin. Anemia, pruritis, neuropathy, pancreatic disease, hyperlipidemia and impotence have each been attributed to elevated PTH in uremia. Critics of the 'PTH is a General Toxin' thesis argue that a statistical correlation of two variables such as PTH and motor nerve conduction velocity is insufficient proof of cause and effect.

To assess the status of our knowledge of the contribution of PTH to both clinical and biochemical pertubations observed in uremia, a group of prime worldwide investigators in the field convened at The Long Island College Hospital in May of 1979. By means of formal lectures, panel discussions and informal interchanges, a comprehensive subject review was effected. Presented herein are the manuscripts which formed the foundation of the conference.

Massry opens with a thorough review of the literature indicating that '... excess PTH is involved in the pathogenesis of many of the manifestations of the uremic syndrome'. *Hawker and DiBella* recount the complexities of measuring so-called active PTH. 'When elevated intact PTH levels in chronic renal failure patients are observed to fall during treatment', they conclude, 'these decreases probably reflect decreases in secretion of biologically active PTH'. While it was appreciated during subsequent discussion that our current means of quantitating PTH carried unproven assumption of hormonal activity, it was nevertheless concluded that measurements of intact PTH were clinically useful.

Rasmussen and Broadus reviewed the interwoven metabolism of PTH and vitamin D. The role of $24,25(OH)_2D_3$ as a feedback modulator of PTH secre-

tion was suggested. According to *Hruska, Martin and Klahr,* PTH stimulates hepatic glucose production which is accompanied by increased alanine uptake by the liver. It was speculated that the PTH-induced glucose release is mediated by enhanced gluconeogenesis. This report provides further evidence of the extraordinarily broad action of PTH.

Progress in the elucidation of the metabolism of PTH was inherent in *Maack and Kau*'s report of renal handling of PTH by perfused normal and nonfunctioning rat kidneys. The kidney is the main organ for catabolism of PTH accounting for about 70% of the plasma disappearance rate at a clearance of 60% of the glomerular filtration rate (GFR). The pertinent finding of *Ichikawa and Brenner* in the Munich-Wistar rat, endowed with a superficial glomerulus, that infusion of bovine PTH reduces GFR raises the possibility that reduced GFR in some hyperparathyroid states might be the consequence of PTH excess. Once more PTH appears as a multispecific organ toxin.

How PTH provokes hypocalciuria was determined in a rat study by *Costanzo and Windhager.* PTH was clearly shown to increase renal distal tubular calcium reabsorption. The question of whether PTH was an important regulator of lipid metabolism was asked by *Heuck and Ritz* who, after analyzing published reports which were 'conflicting and contradictory', concluded that 'the information presently available does not allow any definite conclusions . . .'. In this area, at least, speculation has gone for beyond the limits of hard information.

Measuring PTH impact on the total organism, *Kopple, Cianciaruso and Massry* found that PTH may '. . . cause net protein breakdown due to its direct effects on amino acid metabolism . . .'. These workers called for a study in which prolonged administration of PTH permitted quantification of its action on amino acid, protein and carbohydrate metabolism. *Walser, Mitch and Collier* added to the case against PTH as a toxin in renal disease the thought that progression of chronic renal disease may be factored by intrarenal deposition of calcium and phosphorus because of secondary hyperparathyroidism.

At variance with earlier reports and the concept of PTH-induced tissue calcium deposition was the presentation by *Adler and Berlyne* of multiple tests of brain and skin calcium and magnesium levels in the chronically uremic rat, all of which were depressed. Technical pitfalls in preparing tissues for cation measurements may be responsible for the conflicting earlier reports of increased brain calcium content in uremia. Clearly, unless uniform and reproducible methods are applied, the results of trace metal experiments can be specious and misleading.

A further controversy erupted over the question of PTH interference with electrical conductivity in peripheral motor nerves. *Goldstein and Massry* reviewed the literature including the papers by *Avram* and colleagues and inferred that there is ample '. . . support for a cause and effect relationship between excess PTH and the disturbances of the nervous system in uremia'. *Arieff and Armstrong* could not concur. After analyzing the literature and their own studies

they felt that uremic neuropathy had a complex etiology with '. . . no easily discernable effect of parathyroid hormone . . .'. Further, they stated that if PTH contributes to the encephalopathy of renal failure '. . . it cannot be the only cause'.

Bricker reviewed his pioneering work and emphasized further '. . . a solute specific excretory response per nephron magnified in inverse proportion to the number of residual nephrons' under the influence of PTH. He presented new evidence for 'the probable requirement in both health and chronic renal disease for a "detector oriented" solute specific biologic control system which utilizes PTH as the major effector agent'. *Rosalyn S. Yalow,* the recipient of the Nobel Prize in Medicine for her hormonal bioassay work with parathyroid hormone, urged caution and emphasized 'the complications introduced by the heterogeneity of parathormone' and the controversy concerning the source(s) of the biologically active C-terminal fragment and that 'ectopic production of a peptide resembling authentic PTH may occur in some tumors'.

Finally, *Avram* presented evidence that the degree of pancreatic disease in uremia correlates directly with elevation of measured immunoreactive PTH. In the manuscript, *Avram* presents initial evidence of 'lower parathyroid and creatinine levels in diabetic uremic patients'. He emphasized that the marked neuropathy observed in the peripheral nerve of diabetics with chronic renal failure is 'independent of PTH levels', unlike the decreased nerve conduction which correlated well with increasing PTH levels in the nondiabetic.

By the end of the conference the balance seemed to tilt towards acceptance of PTH as a uremic toxin but by no means the exclusive toxin. Once easier, more precise methods of measurement of proven active PTH are available and standardized techniques for trace metal analysis are extended to local laboratories, the extent to which PTH makes uremic patients sick should be clarified. While awaiting these advances, the concerned investigator need not lack for things to to do as was made evident by these significant new reports provided by all participants in a conference rich in ground-breaking clues for further research in uremia.

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Lower Parathyroid Hormone and Creatinine in Diabetic Uremia

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Introduction

Substantial evidence indicates excess parathyroid hormone (PTH) as responsible for hematologic (1), neurological (2, 3), metabolic (4, 5) and multisystemic (6) pathophysiological abnormalities in uremia. Insulin-dependent diabetics now account for more than 20% of uremic patients treated by maintenance hemodialysis and/or renal transplantation (7). Previously, we studied motor nerve conduction velocity (MNCV) in the peroneal nerve in 12 diabetic patients undergoing hemodialysis and found impaired conduction velocity whether or not PTH was elevated (2). We now extend our observations to a comparison of PTH, MNCV and predialysis serum creatinine to a stable population of diabetic and nondiabetic dialysis patients.

Methods

Patients undergoing maintenance hemodialysis at The Long Island College Hospital were selected for retrospective study on the basis of having had simultaneous (within three days) measurements of PTH and MNCV. A total of 44 subjects, 14 diabetics (group I), and 30 nondiabetic patients (group II), were included in the analysis of patients treated from 1973 until 1978.

Each of the 14 diabetics had documented hyperglycemia and glycosuria preceding the onset of azotemia. Diabetes had been present for a mean of 15.6 years before maintenance hemodialysis was initiated; 4 patients had been diabetic for more than 20 years. Juvenile-onset, insulin-dependent diabetes was present in 5 patients, 2 of whom had renal biopsies showing nodular glomerulosclerosis. Maturity-onset diabetes was the diagnosis in 9 patients, only one requiring insulin therapy. Group I contained 10 men and 4 women of mean age 56.3 ± 1.8 years. Residual creatinine clearance in group I was 1.2 ml/min and 3 patients had zero urine output.

Group II contained 18 men and 12 women of mean age 51.3 ± 2.7 years. None of the group II patients had a history of diabetes or glycosuria; mean predialysis blood glucose

level was 118 ± 11.6 mg/dl with the highest value being 134 mg per deciliter. The renal diagnoses in nondiabetic patients were chronic glomerulonephritis in 10, obstructive uropathy in 3, chronic pyelonephritis in 2, hypertensive renal disease in 3, and polycystic kidneys, gouty nephropathy had multiple myeloma each in 1 patient. No specific diagnosis had been established in the remaining 9 patients.

Parathyroid hormone values were determined predialysis by the method of *Hawker* (8) by Upjohn Laboratories (Kalamazoo, Mich.). None of the patients had undergone partial or complete parathyroidectomy, nor were any being treated with vitamin D or calcium supplements at the time of testing. Mean normal PTH value for the Upjohn Laboratory in 20 healthy adult volunteers aged 20–62 years was 255 pg/ml; normal values included within two standard deviations of the mean ranged from 163 to 347 pg/ml. Predialysis serum creatinine, calcium, and phosphate were measured with an autoanalyzer.

Motor nerve conduction velocity testing was performed using a TECA TE electromyograph (TECA Corporation, White Plains, N.Y.) according to the method of *Johnson and Melvin* as described by *Nielsen*. To standardize results, the value for conduction velocity in the right peroneal nerve was used for all patients. Normal values for peroneal nerve conduction time are 50 ± 6 m/sec. A value of 0 was recorded when no nerve conduction could be recorded after maximal stimulation with 300 V for 1 msec.

All patients were treated with 3 times weekly hemodialysis for 4–6 h employing a coil and a single-pass dialysate flow at 500 ml/min. Calcium concentration in the dialysate was 7.0 mg/dl.

Statistical analysis was performed with the Student's t test for unpaired samples by the N-1 method. Results are expressed as the mean ± standard error of the mean.

Results

Diabetic patients (group I) had a significantly lower ($p < 0.05$) mean predialysis PTH level of 421 ± 67.7 pg/ml than did nondiabetic patients (group II) whose mean PTH was 804 ± 222 pg/ml (table I). Mean predialysis serum calcium levels in group I (8.6 ± 0.32 mg/dl) and group II (8.3 ± 0.2 mg/dl) were similar however. There was no significant difference between predialysis phosphate serum levels in diabetics (4.8 ± 0.4 mg/dl) and nondiabetics (4.2 ± 0.39 mg/dl).

Peripheral neuropathy, as judged by MNCV, was much worse in diabetics (mean MNCV of 20.7 ± 4.8 m/sec) than in nondiabetics (mean MNCV of 36.9 ± 4.7 m/sec; $p < 0.001$). The more debilitated condition of diabetics was also evidenced by a significantly lower mean predialysis serum creatinine (8.8 ± 1.8 mg/dl) than in nondiabetics (10.6 ± 0.62 mg/dl; $p < 0.05$).

Discussion

Since our early report that hemodialysis can prolong life in diabetic uremia (9), clinical nephrologists have learned by experience that uremia in a diabetic tends to be a devastating multisystem illness in which rehabilitation is difficult and frequently unobtainable (10, 11). Our finding of a lower predialysis serum

Table I. Predialysis PTH and serum creatinine in dialyzed diabetics and nondiabetic uremic patients

	Age, years	Calcium, mg/dl	Creatinine, mg/dl	Phosphorous, mg/dl	PTH, pg/ml	MNCV, m/sec
group I, diabetics (n = 14)	56.3 ± 1.8	8.6 ± 0.32	8.8 ± 1.9	4.2 ± 0.39	421 ± 67.7	20.7 ± 4.8
group II, non-diabetics (n = 30)	51.3 ± 2.7	8.3 ± 0.20	10.6 ± 0.6	4.8 ± 0.4	804 ± 222	36.9 ± 4.7

creatinine in diabetics undergoing maintenance hemodialysis as compared to nondiabetics is consistent with our previous report of increased growth hormone levels in this population (12), and can also be attributed to the obviously reduced muscle mass of the catabolic diabetic. We also ascribe the significantly lower MNCV in dialyzed diabetics to their general debilitated state. Both diabetic and uremic neuropathy (13) cause similar histopathological changes including axonal degeneration, Schwann cell proliferation and segmental demyelination which have been attributed to either Schwann cell metabolism (14) or metabolic neuron failure (15). It seems reasonable to speculate that the adverse metabolic effects of uremia and altered parathyroid metabolism in diabetic uremia on neuronal integrity may be additive and even synergistic. At the same degree of renal impairment the diabetic thus has more severe neuropathy. Once established, uremic neuropathy generally does not improve with dialytic therapy (16).

Our finding that the degree of PTH elevation in dialyzed nephropathic diabetics is significantly less than in nondiabetic dialysis patients is not explainable by information now available. A perusal of world literature on the subject lacks any studies of parathyroid hormone in diabetics. Recently, *Wiske et al.* (17) reported increases in immunoreactive parathyroid hormone with age and *Atkinson et al.* (18) an increase of PTH in obese subjects. It has been suggested that body fat increases with age (19) and it is possible that this effect influences parathormone concentration. None of these reports measured parathyroid hormone levels in diabetic or uremic subjects. It is known, however, that other metabolic functions, such as growth hormone, renin, C peptides and insulin may be severly impaired in diabetics (12). A subnormal renin-aldosterone response to a 10- or 20-mEq sodium diet was additionally reported in nephropathic diabetics by *Christlieb et al.* (20) recently, though nonazotemic diabetics had a normal response. Mechanisms which would explain decreased hormonal excretion in diabetics include accelerated microvascular disease in afferent to hypofunctioning endocrine glands or retention of a metabolite which functions as an antagonist to the suppressed hormone.

PTH appears to be a neurotoxin (21). We showed in man (2), as *Goldstein et al.* (22) demonstrate in dogs, that excess PTH will cause a fall in MNCV even

in the absence of uremia. In dialyzed patients the most severe neurological impairment correlated with the highest PTH levels. A paradox is thus noted in the dialyzed diabetic who has lower than nondiabetic PTH levels but greater neurological damage than his nondiabetic counterpart.

In summary, diabetics undergoing maintenance hemodialysis have a lower serum creatinine, lower PTH, and worse motor neuropathy than do non-diabetics undergoing the same treatment regimen. The dual metabolic perturbations of uremia and diabetes are responsible for these changes through a mechanism which has not been elucidated, but in which metabolic aberrations including PTH may play a part.

Summary

Groups of 14 diabetic and 30 nondiabetic patients undergoing maintenance hemodialysis were compared as to levels of serum creatinine, heights of PTH elevation, and finally as to severity of peripheral neuropathy. Diabetics had a statistically lower predialysis serum creatinine, PTH, and MNCV than did nondiabetics. The dual metabolic derangements of uremia and diabetes, along with multiple metabolic aberrations, including PTH, may explain the more severe neuropathy observed in diabetics. A proportionately lower PTH elevation in the diabetic is characteristic of this subgroup of uremic patients.

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