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Cryptococcosis in Renal Transplant Recipient - A Case Report

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Abstract:

A 27 years young male is a known case of live related renal allograft recipient on immunosuppression for last one and half years. Patient was admitted with irregular fever, severe headache, nausea and vomiting in the Department of Nephrology in July 2007. After admission patient was thoroughly evaluated and was clinically diagnosed as meningitis. Subsequent investigation report revealed swelling of 3rd ventricle on CT scan of brain and growth of Cryptococcus in CSF culture. The case was diagnosed as post renal transplant cryptococcal meningitis. Treatment was started with Inj. Amphotericin B along with immunosuppression. But within few days after diagnosis patient went into coma and died.

(Bang. Renal J. 2005; 24(2): 41-42)

Introduction:

Cryptococcosis is the third most common invasive fungal infection in organ transplant recipient after candidiasis and aspergillosis[1]. Literature reports indicate that cryptococcosis usually present as symptomatic disease and despite therapy the mortality remains high[2]. In addition, some data suggest that there might be differences in the incidence and clinical manifestations of cryptococcosis, depending on the specific transplant organ[3]. The incidence of cryptococcosis is significantly higher in heart transplant recipient than in other transplant organ.[3,4] The primary risk factor contributing to cryptococcosis in organ transplant recipient is probably the immunosuppressive therapy used to prevent allograft rejection. Environmental factors may also play a role. Different studies demonstrate differences in the rate of cryptococcosis according to geographic region[4,5].

Moreover, the isolation of the fungus from soil samples with higher concentrations of cryptococcus in areas frequented by birds or contaminated by bird droppings Therefore, it is recommended that organ transplant recipients should avoid birds or areas contaminated with bird droppings.

The organism is trohic to the central nervous system and the majority of the recognized infections in humans cause meningitis[6]. Early studies in kidney transplant recipient during the cyclosporine era found meningitis to be the most common clinical presentation of cryptococcosis[7]. We are reporting here the first case of cryptococcosis in renal transplant recipient in our country.

Case report:

A 27 years young male had history of live related renal transplantation and was on immunosuppression. Patient was admitted in the Department of Nephrology with the complaints of Irregular fever, severe headache and occasional vomiting for one week, restlessness and altered consciousness for two days.

After admission patient was evaluated and clinically found febrile, restless, drowsy, mild hypertensive, nonicteric but evidence of meningeal irritation was found.

Fundoscopic examination revealed bilateral papillodema. Laboratory investigation revealed normal blood count, urine examination showed one + proteinuria, serum creatinine 125 micromol/L, mild hyponatremia which was corrected by normal saline. Blood and urine culture revealed no growth of any organism. X-ray chest was normal, tuberculin test was negative, cytomegalovirus IgM antibody was positive. CSF culture revaled growth of cryptococcus. CT scan of brain showed swelling of 3rd ventricle.

After diagnoiss of ctyptococcosis, lnj. Amphotericin B was started and dose was adjusted according to weight and renal functional status. During the infusion of Amphotericin B occasionally patient developed rigor and high fever. However after 4-5 days patients condition further deteriorated and patient went into coma and ultimately died.

Discussion:

The fungus cryptococcus has CNS tropism and is a common cause of sub acute meningitis. The clinical presentation of cryptococcal meningitis in organ transplant recipients can be quite variable[5]. The most common sign and symptoms of CNS cryptococcosis are encephalopathy

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69%, nausea/vomiting 50%, fever 46%, headache 46%, nuchal rigidity 14%, visual loss 7%, seizure 4%[1]. But in our case all sign and symptoms were present. Radiological imaging of the CNS using CT and MRI scans has shown that the findings in organ transplant recipients with cryptococcal meningitis may be normal or non-specific[4]. In this case CT scan of brain revealed slight bulging of 3rd ventricle but CSF study showed growth of cryptococcus in Indian Ink preparation.

Renal transplant recipients have the lowest incidence of fungal infections compared with other organ transplants[8]. Nevertheless, among cases of transplants with cryptococcosis, renal recipients are relatively common. Several studies on a cyclosporine based regimen reported 3-4% incidence of cryptococcosis. Early studies indicated that the main clinical presentation of the disease was with meningitis, often in a subacute form. But in our case patient presented with acute form of meningitis and died within few days after diagnosis of the disease.

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Original Articles

Microscopic Study of Diameter of the Renal Corpuscle of Bangladeshi People in Different Age Group

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Abstract:

The functional unit of the kidney is the uriniferous tubule, which consists of a nephron, and a collecting duct into which empty the filtered contents of the nephron. The nephron consists of two components, the renal corpuscle and the renal tubule. There are about two millions renal corpuscle in each kidney. A variety of renal disease involving the nephron, involve mostly renal corpuscle. With normal aging there is gradual increase in the size of renal corpuscle with decrease in renal function. It is essential to know the effect of age on functional status of kidney for kidney surgery or transplantation. There were very few known studies about the diameter of renal corpuscle in Bangladeshi people. The study was carried to find out the difference in diameter of renal corpuscle in micrometer in the stained section of kidney in different age group. The collected samples were grouped as A (6-20 yrs), B(21-36 yrs), C (37-65 yrs). The diameter of renal corpuscle per square micrometer were found to be 157.10±5.58 and 154.25±8.90 micrometer in the right and left kidney of group A, 159.18±9.89 and 159.04±8.55 micrometer in the right and left kidney in group B, 175.35±8.84 and 176.58±6.69 micrometer in the right and left kidney in group C. The diameter of renal corpuscle gradually increase with the increasing age but significantly increased after 36 years of age (p<0.014).

Key words: *Kidney, renal corpuscle*

(Bang. Renal J. 2005; 24(2): 27-29)

Introduction:

The kidneys are vital in maintaining homeostasis of the body. They regulate blood pressure, blood composition and fluid volume of the body, produces urine; and maintain acid base balance[1].

Most of the kidney diseases are chronic glomerulonephritis, diabetic nephropathy, hypertensive nephrosclerosis, obstructive uropathy and congenital or familial kidney diseases[2]. Aging is a biologic process from which no life being exempt, and universal effect of aging is the gradual loss of functioning cells from many organs and tissues. The biologic price of aging includes progressive deterioration of renal function and structure. After the age of 30, glomerular filtration and renal blood flow rates decline in a linear fashion. Renal mass similarly declines, and the incidence of sclerotic glomeruli increases with advancing age. Accordingly the aging kidney is at high risk of eventual failure when functioning nephron number is further reduced by acquired renal disease[3]. Renal corpuscle represents the beginning of nephron. In man the renal corpuscle are much more variable in size, diameter ranging from 150-250µm. The size of the renal corpuscle gradually increase along with the increase of age[4]. In our country there was very little histological study with this gland. It has been observed by various workers that diameter of renal corpuscle varies with age[5]. For this reason this study was undertaken to observe the microscopic diameter of renal corpuscle in Bangladeshi people in relation with age.

Materials & Methods:

The study was performed on 50 pair human kidney. All these samples were collected from autopsis in the morgue of the Department of Forensic medicine of Dhaka Medical College and Sir Salimullah Medical College. They were collected from July 2003 to July 2004. The samples were grouped into three age groups according to the study of Darmedy et al (1971)[6] group A(6-20 years), group B(21-36 years) and group C(37- 65 years).The subject covered the age of 6-65 years. The collected samples were washed thoroughly with running tap water and wash kept into 10% formalin solution for preservation and fixation. Six pairs of kidney were selected by random sampling method from each group. Slices of tissue approximately 3 mm. in thickness were taken from cortical regions. From these slices, small rectangular pieces of tissue were taken for microtom section and subsequent processing and then stained with hematoxylin and eosin (H&E) stain.

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Procedure of measurement of diameter of renal corpuscle:

For measurement of the diameter of corpuscle twelve slides from six pairs of kidneys were taken from each group. Thus 36 slides were examined under X10 objectives. From each slide 5 renal corpuscle were chosen. Thus in total 180 different Malpighian corpuscle were observed for measuring diameter of corpuscle (60 from each group). The diameter of the corpuscle was measured by using an ocular micrometer. As the Malpighian corpuscles were not perfectly round or oval in shape, two measurements were taken from each corpuscle. One measurement was taken at the maximum transverse diameter of corpuscle and another one at direction perpendicular to the first one. Thus the transvertical diameters of the corpuscles were measured by taking the mean of two diameters taken at right angles to each other.

Observation and results:

Table-1 and fig-1 shows that the mean (±SD) diameter of renal corpuscle were 157.10±5.58 and 154.25±8.90 micrometer in the right and left kidney of group A, 159.04±8.55 and 159.18±9.89 micrometer in the right and left kidney of group B, 176.58±6.69 and 178.35±8.84 micrometer in the right and left kidney of group C. The mean diameter of renal corpuscle in micrometer was the highest in group C and lowest in group A. There was no significant difference between group A vs. group B but significant difference was found in group A vs. group C and group B vs group C.

Table-I

Diameter of renal corpuscle (micrometer) in different age groups:

Groups	Diameter of Renal corpuscle (Mean ± SD)			
	Right Kidney	Left kidney	Right Kidney	Left kidney
A	157.10 ± 5.58	154.25±8.90	A vs B	Avs B
(n=12)			P = 0.65^{NS}.	P = 0.386 NS
B	159.04±8.55	159.18±9.89	B vs C	B vs C
(n=20)			P = 0.003**	P = 0.005**
C	176.58t6.69	178.35±8.84	A vs C	A vs C
(n-17)			P = 0.003**	P = 0.005**

Significant at $P < 0.05$

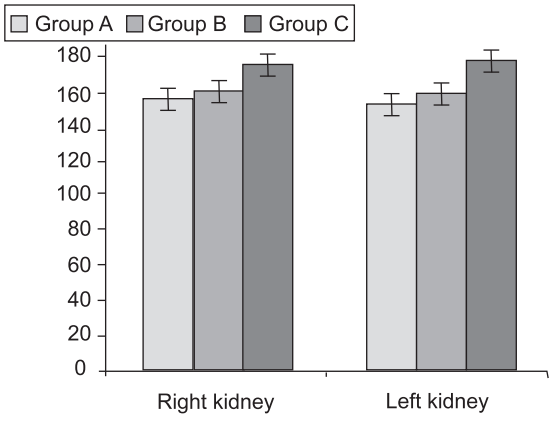

Fig.-1: *Showing the diameter of renal corpuscle of different age group*

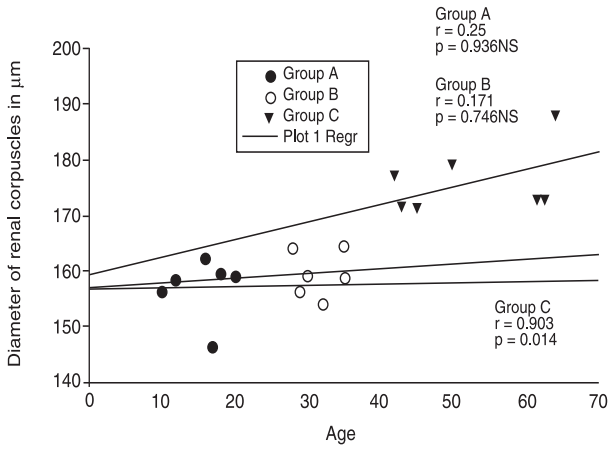

Fig.-2: *Showing the diameter of renal corpuscle in relation to age in year*

Discussion:

Renal corpuscle are much more variable in size. The size of Malphighian corpuscles gradually increases along with the increase of age. It was also observed by Goyal[5], who described that the size of Malpighian or renal corpuscle increased with advancing age or in senile kidneys. Cormack[4] observed that the renal corpuscle is generally ovoid with a diameter of 150 µm to 250 µm. Dunnil et a1[9] observed that the renal corpuscle are small rounded masses, averaging about 0.2 mm in diameter. In present study all the histological sections were taken from cortical region of the kidney. The mean (±SD) diameter of renal corpuscle were found to be 157.10 ±5.58 and 154.25±8.90 micrometer in the right and left kidney in group A, 159.04 ± 8.55 and 159.18 ± 9.89 micrometer in the right and left kidney in group B, 176.58±6.69 and 178.35±8.84 micrometer in the right and left kidney in group C. The diameter of renal corpuscle gradually increased with the increasing age but significantly increased after 36 years of age ($p<0.014$) which was similar with the other studies[7-9].

Conclusion:

In this study it was found that the mean diameter of renal corpuscle in group C was the highest and lowest in group A. Significant difference was found between the diameter of renal compuscle in group A and group C, group B and group C.

The result of the present study will enrich the information pool on the histological status of kidney in Bangladeshi population. Information on the effects of age on renal structure can be obtained from imaging techniques, histological evaluation and micro-dissection studies. Further studies using larger samples covering both sex and wider age range using Resin corrosive cast and angiography are recommended.

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Effect of Calcium Carbonate and Oral Cacitriol on PTH (mid region) in MHD Patients

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Abstract:

Secondary hyperparathyroidsim is common in MHD patients. Sometimes it is difficult to suppres PTH in MHD patient. Oral calcitriol and calcium carbonate therapy can effectively reduce elevated PTH level.A total of 45 MHD (male 24, female 21) patients were prospectively studied in the Department of Nephrology, BSMMU, in collaboration with INM, BSMMU, Dhaka to see the effect of oral calcitriol and calcium carbonate on PTH. Total duration of study was 36 weeks. Initial 4 weeks were washout period; remaining 32 weeks were study period. During this study period all the subjects received calcium carbonate 500mg thrice daily with meal and oral calcitriol 0.25 µg once daily. Serum PTH (midregion), serum calcium, serum alkaline phosphatase, serum Inorganic phosphate, were measured at the end of wash out period, and at 9th months of study period. Elevated serum PTH (mid region), elevated serum alkaline-phosphatase, hyperphosphataemia, hypocalcaemia, was observed at beginning of study and decreased PTH, decreased Inorganic phosphate, decreased alkaline-phosphatase and increased serum calcium level was observed at the end of study period. Median serum PTH (mid region): Beginning of study vs end of study was, 490.56 vs 176.82 pmol/1 (p<0.05). Mean±SD serum alkaline phosphatase: Beginning of study vs end of study was 307.33±133.4 U/L vs 219 .12±86.44 U/L (p<0.01). Mean±SD Serum Inorganic phosphate: Beginning of study vs end of study: 2.60±0.59 mmol/l vs 1.79±0.31 mmol/1(p<0.01). Mean ± SD Serum calcium: Beginning of study vs end of study was 1.92±0.92 mmol/l vs 2.39 ± 0.12 mmol/L (p<0.001). It is concluded that oral calcitriol and calcium carbonate can effectively reduce serum PTH, serum Alkaline phosphatase, serum Inorganic phosphate and elevate serum calcium in MHD patients.

(Bang. Renal J. 2005; 24(2): 30-35)

Introduction:

One of the major hormonal disturbances in uraemia is increased parathyriod hormone (PTH) level[1]. The elevated PTH level occurs early in the course of chronic renal failure (CRF)[2]. Participating in the genesis of many manifestations of uraemic syndrome, the recent available data shows that PTH is a uraemic toxin-and an improvement in many signs and symptoms of uraemia found after a reduction in blood level[3].

PTH is the most important endocrine factor in the regulations of calcium and phosphorous metabolism.

PTH can be measured as intact-(1-84) molecule, amino terminal fragment, carboxy terminal fragment and mid-region fragment.

The mid-region-PTH RIA reads epitopes in the 44-68 region.

Multiple factors in the course of progressive CKD probably contribute to the development of elevated PTH. These factors include hypocalcaemia, hyper-phosphataemia, 1, 25-dihydroxyvitamin D deficiency, down regulation of vitamin D receptor and altered calciums sensing sensitivity[4]. Hypocalcaemia has been shown to increase both the synthesis and secretion of PTH[5]. Hyperphosphosphataemia may directly stimulate parathyroid glands independent of changes of calcium or calcitriol concentration[6]. Reduced level of calcitriol in renal failure will result in chronic excess of PTH[7]. The use of calcitriol in combination with calcium carbonate has gained widespread acceptance in lowering PTH and normalization of calcium level[8].

Calcium carbonate corrects hyperphosphata and calcitriol at a dose of 0.25 ug/day has been shown to reduce PTH

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concentrations to slow down the development of hyperparathyrioidism. Thus, treatment with calcitriol could improve some disorders associated with uraemic syndrome[8,9,10].

In Bangladesh, data regarding PTH in maintenanace haemodialysis patients in relation with different clinical and biochemical parameters are scant[11]. Therefore, the present study was carried out to estimate serum PTH (mid-region) level in maintenance haemodialysis patients as well as effects of calcium carbonate and oral calcitriol on parathyriod hormone.

Subject and methods:

A total of 45 patients (male 24 female 21) suffering from endstage renal disease (ESRD) were randomly selected from haemodialysis unit of nephrology department of BSMMU. They were divided in three groups on the basis of duration of hemodialysis.

Group I: Duration of haemodialysis 6-18 months (n = 12).
Group II: Duration of haemodialysis 19-36 months (n = 20).

Group III: Duration of haemodialysis 37-60 months (n = 13).

Methods

Study design

This was a prospective, randomized clinical study. Total duration of study: 36 weeks, divided into two periods.

1) Initial 4 weeks - washout period.

2) Remaining 32 weeks - study period (calcium carbonate and oral calcitriol therapy).

Washout Period: Duration 4 Weeks

The purpose of 4 weeks washout period was to standardize the diet, dialysate calcium, as well as to lower serum phosphorus concentration to below 6.6 mg/dl. At the end of washout period, fasting blood samples were collected for measurement of different biochemical parameters.

Study Period:

Duration 32 Weeks At the end of washout period, all subjects received oral calcitriol 0.25 microgram once daily and calcium carbonate 500mg thrice daily with meals for 32 weeks.

Biochemical tests were carried out at 9th month of calcium carbonate and oral calcitriol therapy: Serum PTH (midregion) by radioinimunoassay QUA).

- Serum urea
- Serum creatinine (pre-and post-dialysis)
- Serum electrolyte
- Serum calcium
- Serum inorganic phosphate
- Serum alkaline phosphatase

Statistical analysis

Results were expressed as mean ± standard deviation (mean ± SD). Statistical significance of differences between groups were determined by ANOVA and paired student's 't' test. P values less than 0.5 were considered significant.

Observation and Results :

Mean age of MHD patient was (mean ± SD) 40.24±8.94 year of whom male 24, female 21. Table 1 shows distribution of subjects by age in different groups. Table-II shows comparison of serum calcium levels between end of washout period and at 9th month of calcium carbonate and oral calcitriol therapy. Hypocalcaemia was observed in all the groups of MHD patient at the end of washout period. There was significant rise of serum calcium at the end of study period ($P<0.001$) Table III shows elevated serum Inorganic Phosphate levels at the end of wash out period and decreased level of serum inorganic phosphate was found at the end of study period ($P<0.01$) In table IV. Shows raised serum alkaline phosphatase level at the beginning of study and significant reduction of serum alkaline phosphatase was observed at the end of study period ($P<0.05$). Finally table V shows markedly elevated serum PTH (mid region) at the end of washout period, and significant reduction of serum PTH (mid region) at end of calcium carbonate and oral calcitriol therapy ($P<0.01$). Taken together we have shown that 1) Hypocalcaemia 2) Hyperphosphataemia 3) Raised serum alkaline phosphatase level 4) Raised serum PTH (mid region) level at the beginning of calcium carbonate and oral calcitriol therapy and Increased serum calcium level,decreased serum Inorganic phosphate level, alkaline phosphatase level and serum PTH (mid region) level at the end of calcium carbonate and oral calcitriol therapy.

Table-I

Distribution of subjects by age in different groups

Parameters	Group I (n=12)	Group II (n=20)	Group III (n=13)	Total (n=45)
Duration of haemodialysis (months)	6-18	19-36	37-60	6-60
Age (years)	40.75	43.10	35.38	40.24
(Mean± SD)	±10.80	±7.20	±8.06	±8.94

Table-II

Comparison of serum calcium levels between end of washout period and at 9th month of calcium carbonate and oral calcitriol therapy.

Duration of haemodialysis	Mean ± SD (mmo/L)	Range (mmol/L)	P value
Group I: 6-18 m (n=12)			
At end of washout	1.85±0.32	1.50-2.50	
versus at 9th month	2.37±0.10	2.21-2.54	0.000***
Group II: 19-36 m (n=20)			
At end of washout	1.94±0.30	1.20-2.50	
versus at 9th month	2.43±0.10	2.26-2.62	0.000***
Group III: 37-60m (n=13)			
At end of washout	1.96±0.27	1.60-2.50	
versus at 9th month	2.36±0.16	2.12-2.61	0.000***

* Significant at P < 0.05
** Significant at P < O.OI
***Significant at P < 0.001

Table-III

Comparison of serum inorganic phosphate levels between end of washout period and at 9th month of calcium carbonate and oral calcitriol therapy

Duration of Haemodialysis	Mean ± SD (mmo/L)	Range (mmol/l)	P value
Group I 6-18 m (n=12)			
At end of washout	2.60±0.61	1.30-3.30	
versus at 9th month	1.80±0.27	1.30-2.14	0.000***
Group II: 19-36 m (n=20)			
At end of washout	2.71±0.49	1.95-3.72	
versus at 9th month	1.82±0.24	1.20-2.30	0.000***
Group 111: 37-60 m (n=13)			
At end of washout	2.48±0.67	1.69-3.82	
versus at 9th month	1.94±0.40	1.48-2.61	0.022*

Ns Not significant
* Significant at P < 0.05
***Significant at P < 0.001

Table-IV

Comparison of serum alkaline phosphatase levels between end of washout period and at 9th month of calcium carbonate and oral calcitriol therapy.

Duration of haemodialysis	Mean ± SD (mmol/L)	Range (mmo/L)	P value
Group I 6-18 m (n-12)			
At end of washout	315.50±150.64	118.00 - 640.00	
versus at 9th month	214.92±86.68	107.00 - 421.00	0.041 *
Group 11: 19-36 m (n=20)			
At end of washout	305.34±155.02	172.00 - 687.00	
versus at 9th month	221.75±96.16	120.00 - 508.00	0.040*
Group III: 37-60 m (n-13)			
At end of washout	302.85±94.54	188.00 - 486.00	
versus at 9th month	220.69±79.48	105.00 - 401.00	0.017*

NS Not significant
• Significant at P < 0.05
***Significant at P < 0.001

Table-V

Comparison of serum PTH (midregion) levels between end of washout period and at 9th month of calcium carbonate and oral calcitriol therapy

Duration of haemodialysis	Mean ± SD (mmol/L)	Range (mmol/L)	P value
Group I: 6-18 m (n=12)			
At end of washout	544.19	192.60-1656.74	
versus at 9th month	206.31	71.70-780.20	0.021 *
Group II: 19-36 m (n=20)			
At end of washout	476.82	155.60-1850.41	
versus 9th month	196.12	56.02-1425.36	0.032*
Group III: 37-60 m (n=13)			
At end of washout	440.68	96.24-3119.93 versus	
versus 9th month	128.02	43.96-1178.46	0.087NS

NS Not significant
•Significant at P < 0.05
***Significant at P < 0.001

Discussion:

The present study was undertaken to observe the effect of calcium carbonate and oral calcitriol on parathyroid hormone in maintenance haemodialysis patients. In this study, serum PTH (midregion) was measured at the end of washout period and at 9th month of calcium carbonate and oral calcitriol therapy. It has become evident that significant rise of serum PTH (midregion) was found at the end of washout in all groups. It was 7-8 times above the normal level (<70 pmol/L). At 9th month of calcium corbonate and oral calcitriol therapy, there was satistically significant reduction of serum PTH (P<0.05.) Wide variations of serum level was observed in maintenance haemodialysis patients. The finding was similar with previous study. Secondary hyperparathyroidism is prevalent in patients with ESRD and maintenance haemodialysis[12]. Two major factors responsible for the development of secondary hyperparathyroidism are phosphorus retention and diminished 1,25, $(OH)_2D_3$. -The effect of diminished $1,25(OH)_2D_3$ is hypocalcaemia. Thus, correction of both hypocalcaemia and hyper-phosphataemia is crucial in the treatment of secondary hyperparathyroidism[13]. The most commonly used calcium salts as phosphate binders are calcium carbonate and calcium acetate. The dosage of calcium carbonate vary from 1.5 to 12 g/day. Large dosages are associated with over-suppression of PTH and development of adynamic bone disease. A relative or absolute deficiency of $1,25(OH)_2D_3$ exists in those with advaned renal failure and maintenance haemodialysis patients. In several controlled trials, calcitriol at a dose of 0.25 μg /day or more has been shown to reduce PTH concentration and slow down the development of hyperparathyroidism[14]. In this study, it was observed that all the subjects in three groups were hypocalcaemic at the end of washout period. Serum calcium level of MHD patient depends upon several factors. These include dietary factor, ingestion of calcium containing phosphate binder, calcitriol therapy and dialysate calcium concentration. Dialysate calcium concentration is an important factor for maintaining serum calcium level in MHD patients. In our centre, dialysate calcium concentrate was 1.8 mmol/L. Despite this, hypercalcaemia did not develop in our study population, because our patients received a physiological dosage of calcium carbonate (500 mg, thrice daily) and oral calcitriol (0.25 ug, once daily). When compared the serum calcium of different groups between end of washout period and 9th month of study period, increase serum calcium level was observed in all groups at the end of study period.

It was observed that serum inorganic phosphate levels were significantly higher in all the groups of MHD patients at the end of washout period. Serum inorganic phosphate levels were significantly decreased at 9th month of Study period.

Walling (1977) showed that hyperphosphataemia in dialysis patients has been shown to be a major factor in worsening of hyperparathyroidism[15]. As the search for a substitute for non- Aluminum containing binders intensified, calcium carbonate has become the alternative binder. It was observed that serum alkaline phosphatase levels were elevated in all the three groups at the end of washout period. Significant decrease was obseved at 9th months of study period in all subjects of three groups. Although serum alkaline phosphatase levels are nonspecific investigations for renal osteodystrophy, they do show good correlations with osteoid accumulation in the skeleton[16]. The measurement of bone-specific alkaline phosphatase is more sensitive and specific than total alkaline phosphatase, but this is expensive[17].

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Genetic Association with Diabetic Nephropathy – A Review

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Abstract:

Diabetic nephropathy (DN) develops in variable numbers of patients with type 1 and type 2 diabetes. A number of factors increase the risk of nephropathy that includes haemodynamic disturbance, hypertension, growth factors, cytokines and genetic factors. The genetic predispositions for the development of DN have been postulated owing to its familial aggregation. Genetic inheritance may play an important role in the development of diabetic nephropathy in both type 1 & type 2 diabetic subjects. These genetic factors may be responsible and explain why some of the diabetic patients are vulnerable where as some are not to nephropathy, irrespective of their diabetic control. Studies showed significant association of insertion/deletion (1/D) polymorphisms in angiotensin converting-enzyme gene with susceptibility to micro vascular complications in both type 1 & type 2 diabetic patients. Angiotensinogen gene TT polymorphism also been suspected to be an independent risk factor of diabetic nephropathy. Similarly some other genes have been studied in different designs to identify if there is any positive association of nephropathy with genetic makeup. However their exact nature of involvement yet to be clearly understood.

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Introduction:

Approximately 30-40% of all type I and type 2 diabetic patients may develop diabetic nephropathy [1].Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, progressive decline in glomerular filtration rate, raised arterial blood pressure, and high relative mortality from cardiovascular and renal disease. The pathogenesis of this complication is not fully understood, but present evidence suggests a multi-factorial origin with contributions from haemodynamic alterations, metabolic abnormalities, various growth factors and genetic factors [2, 3].The prevalence of diabetic nephropathy varies with ethnic background. Pima, Navajo, Winnebago and Omaha Indians show the highest prevalence [4]. Caucasians of European origin demonstrate the lowest prevalence [5]. The prevalence of type 2 diabetic nephropathy in African-Americans is four times higher than in a population of non-Hispanic whites [6, 7].

Lead to Genetic Basis:

The causes for the pathogenesis of diabetic nephropathy are to be looked for within the pathogenesis of diabetes itself. Around 400-600 B.C. Characa and Sushruta, considered two causes for the sweet urine: (1) genetic (in the sense of transmission from generation to generation over the semen) and (2) environmental (in the sense of an inappropriate diet) [8]. Modern definition is based on this early observation: the pathogenesis of diabetes and diabetic nephropathy is promoted by an individual genetic predisposition (activity, diet, overweight, climate and metabolic control) in its phenotypic expression (complex disease).

In 1933 Pincus and White [9] observed that 10-30% of first-degree relatives of diabetic patients had diabetes, whereas diabetes occurred only in 1-6% of first degree relatives of nondiabetic subjects. Subsequent studies also strongly supported a genetic predisposition for type 2 diabetes and nephropathy. Nephropathy in type 1 diabetes is shown to be independent of metabolic control. A significant number of diabetic patients did not develop diabetic nephropathy despite long-term severe chronic hyperglycemia. Therefore, it has been suggested that a subset of patients with type 1 diabetes developed nephropathy due to nonmetabolic (hereditary) factors [10].

Some families with several diabetic patients presented almost no clinical signs of diabetic nephropathy, whereas 80% of the diabetic patients from other families developed diabetic nephropathy. The high variance indicates the contribution of environmental and genetic heterogeneity[4]. Siblings of type 1 diabetic patients with nephropathy have a higher risk of developing diabetic nephropathy[11, 12]. The rate of relatives of type 2 diabetic patients developing ESRD is five times higher (37%) than in relatives of type 2 diabetic patients without nephropathy [13]. If both parents present with diabetic nephropathy, the disease was observed in 46% of the offspring's. In contrast, only 23%

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of the offspring's progressed to diabetic nephropathy if only one parent was proteinuric and 14% if none of the parents had proteinuria[4].

Studying Pathogenesis Phenotypically:

The clinical outcome of diabetes and nephropathy varies remarkably. The involvement of multiple organ systems in the pathogenesis implicates that possible genetic defects can be of a complex nature. Therefore, more than one gene could be affected [14] .Until 10 years ago, genetic studies were difficult to perform because of too few genetic markers and lacking the appropriate analysis methods. Therefore, scientists were focusing on the phenotypic side of a disease background.

Chronic hyperglycemia leads to the generation of advanced nonenzymatic glycated end products (AGE) and to the activation of proteinkinase C isoforms in the vessel wall. This activates a cascade of vessel injuring events and further activates the aldose reductase pathway [15]. The result is a toxic accumulation of sorbitol in kidneys of diabetic patients. Furthermore, AGEs activate signaling transmission pathways generating pathologic accumulations of extracellular matrix (ECM) in the mesangium obstructing capillary lumina. The result is renal failure leading to ESRD and dialysis [16]. Mesangial cell cultures in media with high glucose concentration or AGEs produce more growth hormone (HGF) mRNA and demonstrate an increase synthesis of ECM mRNA and proteins. Mesangial cell cultures over expressing glucose transporter 1 (GLUT1) generate more collagen mRNA and proteins in high-glucose medium [17, 18]. Under in vitro conditions glucose, AGEs, angiotensin II, and endothelin increase the expression of transforming growth factor [19] .Transforming growth factor promotes the pathogenesis of diabetic nephropathy by affecting the interaction of hemodynamic and metabolic factors, leading to an increased ECM synthesis. The role of other cytokines like the vascular endothelial growth factor is being investigated.

Search for Genetic Markers:

Phenotypically oriented research has not led to a breakthrough in revealing the pathogenesis of diabetic nephropathy. The development of a high-resolution micro-satellite marker map with thousands of markers over the last 10 years enabled larger genetic association and linkage studies. Until that time, these studies were carried using only a few restriction fragment polymorphisms. Sometimes the heterogeneous clinical picture of diabetes aggravates the decision whether the doctor deals with a type 1 or a type 2 diabetic patient. At the present time, subjects at risk among the offspring's of diabetic patients cannot be identified by biochemical or a genetic test. The heterogeneous clinical outcome is probably due to genetic heterogeneity. Many different genes influence the susceptibility to develop diabetes or diabetic nephropathy. This is supported by the identification of overlapping subgroups of patients with different phenotypes in the Decode Study [20, 21]. Due to the lower life expectancy and the late age at diagnosis of type 2 diabetes, the parents of affected individuals are mostly not alive. Because of the lack of extended pedigrees, it is not possible to perform linkage analyses.

Association Studies (Case-Control Studies) – Examples and Pitfalls

For a long time scientists have focused on association of candidate gene variants, either in coding and noncoding sequence, with diabetic nephropathy. The simplicity of such a study design with involvement of related patient and healthy individual without the necessity of collecting large pedigrees was intriguing. Candidate gene studies based on association designs have rarely been successful.

What can a positive association implicate in regard to the disease? A positive association can occur if the tested allele cases the disease. In this case one would expect to find the same association in all investigated populations because the mutation triggers the disease (assuming identical phenotypes without phenocopies). A positive association can also occur if allele A does not cause the disease but is in linkage disequilibrium with the 'true' variant. Positive associations could also be caused by an artifact of an admixed population. In an admixed population, every disease which occurs with the same prevalence in each of the populations ethnic sub-units could be positively associated with every allele which occurs at a higher frequency in cases compared to controls [22].

In the case of diabetes and diabetic nephropathy, where both traits are a result of interplay of many genes, the influence of a specific gene and the prevalence of a given single nucleotide polymorphism may vary between different populations. This is finally due to the evolution of man, due to the migration out of Africa resulting in inhomogeneous distributions of founder mutations in different populations around the world. To avoid false-positive associations, only relatively homogeneous populations should be tested. A positive association from

a large, admixed population, which was not replicated in homogeneous groups, could be an artifact of an admixed population. Therefore Hardy Weinberg equilibrium is essential for association studies. In some cases one would identify subgroups with a different ethnic background. For a more correct analysis, those groups must be analyzed separately. Good association studies must contain functional data. The control group should not contain potential at-risk subjects. That is not an easy task given the complexity of most multi-factorial diseases. Because of the size of the population and therefore, the amount of meioses and crossing over, the responsible linkage dis-equilibrium would extend over such a short distance that one must test thousands markers in order to be successful with this particular method.

Linkage Study and Genome Scan:

For linkage studies extended pedigrees are required. In principle, one focuses on the inheritance of a specific trait within families. For genome scans, candidate genes are not of interest. Polymorphic genetic markers with known positions and spaced in smaller intervals along the entire genome are used. The aim is to identify a pathogenetically important region. This hot region is being transmitted together and, therefore, 'linked' with a specific disease in the next generation with a family. Therefore, linked markers indicate this gene region. In a next step, candidate genes will be looked for within the linked regions.

Polygenic Diabetes with Diabetic Nephropathy:

Type 2 diabetes is a polygenic disease. It is very likely that an interplay of specific allele constellations of various 'diabetogenic' polymorphisms in different genes or regulatory elements makes the blood glucose regulation system more or less tolerant of environmental factors like overweight and stress. These polymorphisms may occur at fairly high frequencies within the population. By looking at each one of them separately, the allele frequencies do not need to differ significantly between cases and controls. One single polymorphism can barely be responsible for the development of type 2 diabetes.

For the analysis of diabetic nephropathy, there are only a few genetic linkage studies. The case numbers were always too small; therefore, the size of the sample could not be considered as being representative. A genome wide scan in affected type 2 diabetic sib pairs with diabetic nephropathy revealed four linked regions: the regions on chromosomes 7 and 20 were only linked with nephropathy, and chromosomes 3 and 9 showed linkage with nephropathy and retinopathy. The sample size of 98 affected sib pairs in this study was also very small [23]. Recently, a new nephropathy locus was identified in 18 large Turkish families on chromosome 18q 22.3-23 and confirmed in 101 affected sib pairs of Pima Indians [24].

Human ACE I/D polymorphism associate with progression of diabetic Nephropathy:

Studies of familial clustering [25-27] and genetic predisposition [28-29] suggest that genetic factors are involved in the pathogenesis of diabetic nephropathy. One candidate gene is the gene coding for ACE in which an insertion/deletion polymorphism (ACE/ID) has been described [30]. Based on the presence [insertion (I)] or absence [deletion (D)] of a 287 bp sequence in intron 16, three genotypes are found (DD and II homozygotes and ID heterozygotes). The DD subjects (diabetic [30, 31] or non-diabetic [30]) are characterized by a mean plasma/serum ACE level approximately double that of II subjects, with ID subjects having intermediate values. Furthermore, this polymorphism has been associated with an increased risk of coronary heart disease both in non-diabetic [33] and diabetic populations [34,35].In diabetes, the initial report from Marre *et a*l.[31] proposed a protective effect of the II genotype against development of diabetic nephropathy in insulin dependent diabetes (IDDM). Since then, a substantial number of association studies have been conducted to investigate the possible relationships between elevated urinary albumin excretion rate and the ACE/ID polymorphism in patients with either IDDM or non-insulin-dependent diabetes (NIDDM).

The association of the I/D polymorphism with cardiovascular disease has also been firmly established in a meta-analysis of all available studies [36]. Studies on the I/D polymorphism in renal diseases have suggested that it is a risk factor for the progression, but not for the initiation of renal disease. The ACE genotype frequencies in two studies of patients with IgA nephropathy for instance were similar to those in the general population. However, the DD genotype in those studies was more prevalent in patients with a rapid decline of renal function[37]. This association of the DD genotype with the progression of renal disease has since been demonstrated by others, both in patients with IgA nephropathy and in patients with other diseases. This issue of an association of the DD genotype with the progression of renal disease has remained unresolved in patients with diabetic nephropathy due to IDDM until now. Four recent meta-analyses on the subjects with two of them claiming an

association and two disclaiming it [38]. However, these studies have defined diabetic renal disease as the presence of macroalbuminuria, progressive renal failure or end stage renal disease thereby not taking into account that patients with microalbuminuria. Microalbuminuria do not always progress to macroalbuminuria with associated decline of renal failure and that some of them might even regress to normoalbuminuria [39]. One would have to include cases with progressive renal failure only to resolve the issue. It may therefore be hypothesized that the DD genotype is a risk factor for the progression and not for the initiation of diabetic nephropathy similar to its effect in other renal diseases.

Relationship between angiotensinogen gene M235T variant and diabetic nephropathy:

The renin-angiotensin system (RAS) plays a central role in the maintenance of vascular tone and may be an important contributor to the diabetic macroangiopathy as well as microangiopathy [40]. In humans, AGT gene is situated on chromosome 1q42-43, 12 kilo bases long and consists of five exons interrupted by four introns, as a single copy in the human genome. A molecular variant involving a methionine to threonine transition at amino acid position 235 (M235T) has been described and the polymorphism has been associated with essential hypertension in a number of cross-sectional studies. Recently, the association of the RAS gene polymorphism with nephropathy was reported in diabetic patients e.g. angiotensin 1 converting enzyme (ACE) gene and angiotensinogen (AGT) gene [41,42] suggesting that the polymorphism confers susceptibility to diabetic nephropathy.Fogarty *et al*.[42] reported that a molecular variant of AGT is associated with diabetic nephropathy in IDDM, but there was no similar study in NIDDM.

Genetic inheritance play an important role in the development of diabetic nephropathy in both type 1 and type 2 diabetic subjects. These genetic factors may be responsible and explain why some of the diabetic patients are vulnerable and some are not to diabetic nephropathy, irrespective of their glycemic control.

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Abstracts From Current Literature

Lipid peroxidation in IgA nephropathy and the effect of lipo-prostaglandin E1.

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Background: Lipid peroxidation (LPO) plays a role in glomerulonephritis pathogenesis. The role of LPO in IgA nephropathy (IgAN) and the effect of prostaglandin E1 on it, is not determined. METHODS: Levels of malondialdehyde (MDA), superoxide dismutase (SOD) and vitamin E (vitE) were measured in 42 patients with IgAN and in 31 healthy controls. Clinical nephropathy parameters such as daily proteinuria (DP), serum creatinine (Cr) and Cr clearance were obtained. Forty-two IgAN patients were divided into two subgroups according to renal pathology severity. Twenty-one patients with IgAN received lipo-prostaglandin E1 (PGE1) treatment and the other 21 patients received saline as a control. Results: The serum activity of SOD and vitE in IgAN patients was significantly lower than in healthy controls, while the MDA level was higher in the patient groups. DP-related positively to MDA, while it related negatively to SOD and vitE. Cr clearance related negatively to MDA, while it related positively to SOD and vitE. In the moderate pathological group, the MDA level was significantly higher and the SOD activity was lower than in the mild pathological group. The MDA level in the PGE1 treated group was lower than in the control group, but the activity of SOD and vitE did not differ significantly from the control group. DP declined and Cr clearance increased in the PGE1 treated group, while no significant change in serum Cr was noted. Conclusions: LPO in IgAN was evident and was at least attributed to the decline in antioxidant ability. LPO could play a role in IgAN pathogenesis, and PGE1 is able to ameliorate the LPO in IgAN patients.

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Randomized, controlled study of the effects of losartan versus enalapril in small doses on proteinuria and tubular injury in primary glomerulonephritis.

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Background: Pharmacological blockade of the renin-angiotensin-aldosteron system ameliorates glomerular and tubulointerstitial damage. For optimal renoprotection, high doses of angiotensin II converting enzyme inhibitors and angiotensin II subtype 1 receptor antagonists are commonly recommended, but cannot always be administered. The aim of this study was to evaluate the effects of low-dose (25 mg) losartan on proteinuria and tubular injury extent. MATERIAL/METHODS: This was an open, randomized, 12-month study on the effects of 25 mg of losartan (n=19) vs. 10 mg of enalapril (n=14) as a control on proteinuria, urinary excretion of N-acetyl-beta-D-glucosaminidase (NAG), and blood pressure in patients with primary glomerulonephritis. The second part of the study was an uncontrolled assessment of the renal effects of 50-mg administration of losartan. RESULTS: There were no significant differences between the groups in the effects on proteinuria and NAG excretion. Losartan and enalapril reduced proteinuria by 32.8% ($p<0.029$) and 40.9% ($p<0.021$), respectively, but did not affect NAG excretion. The antiproteinuric effect of losartan, achieved without changes in blood pressure, was particularly evident in subjects with proteinuria >1.5 g/24 h and normal blood pressure. 50 mg of losartan caused a significant decrease in NAG excretion vs. the baseline ($p<0.027$). CONCLUSIONS: 25 mg of losartan and 10 mg of enalapril equally reduce proteinuria. The significant antiproteinuric effect of losartan was achieved despite no changes in blood pressure. There were no differences between the drugs regarding their influence on tubular injury extent. 50 mg of losartan seems to be the minimal dose to improve tubular status.

Med Sci Monit. 2005 Apr;11(4):PI31-7. Epub 2005 Mar 24.

Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis

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Mycophenolate mofetil (MMF) and the sequential use of cyclophosphamide followed by azathioprine (CTX-AZA) demonstrate similar short-term efficacy in the treatment of diffuse proliferative lupus nephritis (DPLN), but MMF is associated with less drug toxicity. Results from an extended long-term study, with median follow-up of 63 mo, that investigated the role of MMF as continuous induction-maintenance treatment for DPLN are presented. Thirty-

three patients were randomized to receive MMF, and 31 were randomized to the CTX-AZA treatment arm, both in combination with prednisolone. More than 90% in each group responded favorably (complete or partial remission) to induction treatment. Serum creatinine in both groups remained stable and comparable over time. Creatinine clearance increased significantly in the MMF group, but the between-group difference was insignificant. Improvements in serology and proteinuria were comparable between the two groups. A total of 6.3% in the MMF group and 10.0% of CTX-AZA-treated patients showed doubling of baseline creatinine during follow-up (P = 0.667). Both the relapse-free survival and the hazard ratio for relapse were similar between MMF- and CTX-AZA-treated patients (11 and nine patients relapsed, respectively) and between those with MMF treatment for 12 or >/=24 mo. MMF treatment was associated with fewer infections and infections that required hospitalization (P = 0.013 and 0.014, respectively). Four patients in the CTX-AZA group but none in the MMF group reached the composite end point of end-stage renal failure or death (P = 0.062 by survival analysis). It is concluded that MMF and prednisolone constitute an effective continuous induction-maintenance treatment for DPLN in Chinese patients.

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Renoprotective effect of diltiazem in hypertensive type 2 diabetic patients with persistent microalbuminuria despite ACE inhibitor treatment.

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The aim of the study was to evaluate the effects of the non-dihydropyridine calcium antagonist (NDCA) diltiazem on the development of urinary albumin excretion (UAE) in type 2 hypertensive diabetic patients with persistent microalbuminuria despite ACE inhibitor treatment. Thirty-six type 2 diabetic hypertensive patients with microalbuminuria persisting after at least 1 year of treatment with ACE inhibitors were randomized to receive captopril (n=22) or combined therapy with captopril and 120 mg diltiazem (n=14) for 2 years. Captopril dose was individualized according to blood pressure. Changes in UAE, blood pressure, and metabolic control were monitored to analyze the influence of the addition of diltiazem on progression of diabetic nephropathy. In patients treated with captopril and diltiazem, absolute UAE did not change during the study (baseline: 101 mg/24 h, range 39-298; 2 years after randomization: 74 mg/24 h, range 12-665). In contrast, UAE increased in patients treated with captopril monotherapy (baseline: 118 mg/24 h, range 32-282; 2 years after randomization: 164 mg/24 h, range 15-1161, p<0.05). In addition, fewer patients in the captopril/diltiazem group progressed to macroalbuminuria (eight patients in captopril group and one in captopril/diltiazem group, p<0.05). The beneficial effects of the addition of diltiazem were independent of blood pressure and metabolic control. We suggest that the combination of ACE inhibitors and NDCA should be considered in type 2 microalbuminuric patients at high risk for progression to established diabetic nephropathy.

Diabetes Res Clin Pract. 2005 Oct;70(1):13-9. Epub 2005 Apr 15.

Stabilization and regression of albuminuria in Chinese patients with type 2 diabetes: a one-year randomized study of valsartan versus enalapril.

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This study was designed to compare the short-term (1-y) tolerability and antiproteinuric efficacy of enalapril and valsartan in patients with type 2 diabetes. Forty-two patients with normal renal function or early-stage nephropathy were recruited in Hong Kong and randomized to valsartan 80 mg/day or enalapril 5 mg/day; the doses were increased to 160 mg and 10 mg daily, respectively, as tolerated. Early-morning urine was analyzed for albumin and creatinine and 24-hour urinary albumin excretion at baseline and 1 year after therapy began. Twenty-two patients were randomized to valsartan and 20 to enalapril. The 2 treatment groups were similar in terms of age, sex distribution, and duration of diabetes or hypertension. Blood pressure decreased to a similar extent (-2.5% to -5.0%) with each drug. Similarly, the 24-hour urinary albumin excretion decreased by 5% to 6% with each drug. The albumin-creatinine ratio in early-morning urine samples and plasma creatinine levels decreased in the valsartan group and increased in the enalapril group, but the difference was not significant. Plasma potassium levels were stable in both groups at the end of study.

Cough was reported by 7 (35%) patients receiving enalapril and none of those receiving valsartan (P=.003). In conclusion, enalapril and valsartan both reduced blood pressure and albuminuria to a similar extent with 1 year of therapy in Chinese patients with type 2 diabetes and normal renal function or early-stage nephropathy. Fewer adverse events were reported with valsartan, but both drugs appear to be relatively safe.

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Dual blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy: the role of aldosterone.

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Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with both ACE inhibitors and angiotensin II receptor-blockers has been shown to reduce both albuminuria and blood pressure compared to either monotherapy. The mechanisms behind these beneficial effects are not known, and we hypothesized that the effect of dual RAAS blockade may be due to a more complete suppression of circulating aldosterone. We performed a combined analysis on three randomized, double-masked, cross-over trials where 51 type 1 diabetic patients suffering from diabetic nephropathy received 8 weeks of dual RAAS blockade using an angiotensin II receptor blocker in combination with an ACE inhibitor and 8 weeks of monotherapy with the same ACE inhibitor. Albuminuria, 24 h blood pressure, GFR, and plasma aldosterone were determined at the end of each treatment period. Compared to ACE inhibition alone, dual RAAS blockade lowered blood pressure by 7/5 mm Hg from 137/76 mm Hg, decreased albuminuria by 37% from 558 mg/24 hour, and reduced plasma aldosterone by 28% from 59 pg/ml and caused a reversible decline in GFR of 4 ml/min/1.73 m2 ($p < or = 0.01$ for all comparisons). There was and a significant correlation between changes in 24-hour diastolic blood pressure and changes in albuminuria. Furthermore, the antialbuminuric response to dual blockade was influenced by the ACE/ID polymorphism, that is, patients carrying the D-allele had a significantly lower reduction of 31% compared to the 55% in patients with the II genotype ($p = 0.021$). Multiple linear regression analysis revealed that ACE/ID genotypes and reduction in plasma aldosterone, diastolic blood pressure and GFR is associated with changes in albuminuria on dual blockade treatment (R2 (adjusted) = 0.57, $p < 0.001$). Dual RAAS blockade is a new treatment concept that may offer additional cardiovascular and renal protection in type 1 diabetic patients with diabetic nephropathy. The beneficial response may be influenced by genetic factors and reductions in blood pressure and plasma aldosterone concentrations.

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Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease.

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It is unclear whether physiologic hemoglobin targets lead to cardiac benefit in incident hemodialysis patients without symptomatic heart disease and left ventricular dilation. In this randomized, double-blind study, lower (9.5 to 11.5 g/dl) and higher (13.5 to 14.5 g/dl) hemoglobin targets were generated with epoetin alpha over 24 wk and maintained for an additional 72 wk. Major eligibility criteria included recent hemodialysis initiation and absence of symptomatic cardiac disease and left ventricular dilation. The primary outcome measure was left ventricular volume index (LVVI). The study enrolled 596 patients. Mean age, duration of dialysis therapy, baseline predialysis hemoglobin, and LVVI were 50.8 yr, 0.8 yr, 11.0 g/dl, and 69 ml/m2, respectively; 18% had diabetic nephropathy. Mean hemoglobin levels in the higher and lower target groups were 13.3 and 10.9 g/dl, respectively, at 24 wk. Percentage changes in LVVI between baseline and last value were similar (7.6% in the higher and 8.3% in the lower target group) as were the changes in left ventricular mass index (16.8 versus 14.2%). For the secondary outcomes, the only between-group difference was an improved SF-36 Vitality score in the higher versus the lower target group (1.21 versus -2.31; $P = 0.036$). Overall adverse event rates were similar in both target groups; higher ($P < 0.05$) rates of skeletal pain, surgery, and dizziness were seen in the lower target group, and headache and cerebrovascular events were seen in the higher target group. Normalization of hemoglobin in incident hemodialysis patients does not have a beneficial effect on cardiac structure, compared with partial correction.

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A large, prospective, randomized, open-label, multicentre study of corticosteroid withdrawal in SPK transplantation: a 3-year report

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Background: Simultaneous pancreas-kidney (SPK) transplantation is the treatment of choice for selected diabetic patients. Corticosteroids are an important element of immunosuppressive protocols, but their long-term use has detrimental effects on patients' health, necessitating eventual discontinuation. METHODS: This prospective study evaluated the safety and feasibility of corticosteroid withdrawal in 205 SPK transplant recipients randomized to immunosuppressive treatment with either tacrolimus and mycophenolate mofetil (MMF) (n = 103) or cyclosporin microemulsion (ME) and MMF (n = 102). RESULTS: Corticosteroid withdrawal was successful in the majority of in-study patients (66% tacrolimus, 73% cyclosporin-ME). Compared with out-of-study patients or those continuing corticosteroid therapy, in-study patients withdrawn from corticosteroids experienced fewer pancreas or kidney graft losses, fewer episodes of acute rejection and were less likely to be withdrawn from the study. Acute rejection occurred after corticosteroid withdrawal in two patients who had a previous rejection and in five patients who were rejection-free before corticosteroid withdrawal. No rejection episodes were associated with graft loss or immediate serious consequences. Overall, corticosteroid withdrawal was achieved with an increase in the dose of both MMF and tacrolimus. CONCLUSIONS: A long-term survey of corticosteroid withdrawal in SPK transplantation with multifactorial analyses is necessary to confirm these early results and to evaluate the positive effects on glucose metabolism and hypertension.

Nephrol Dial Transplant. 2005 May;20 Suppl 2:ii40-7, ii62.

Teaching and motivating patients to control their risk factors retards progression of cardiovascular as well as microvascular sequelae of Type 2 diabetes mellitus- a randomized prospective 8 years follow-up study.

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AIMS: To examine whether motivating patients to gain expertise and closely follow their risk parameters will attenuate the course of microvascular and cardiovascular sequelae of diabetes. METHODS: A randomized prospective study on 165 patients with diabetes mellitus Type 2, hypertension (> 140/90 mmHg) and hyperlipidaemia (LDL-C > 3 mmol/l), referred for consultation to a diabetes clinic in an academic hospital. Patients were randomly allocated to standard consultation (SC) or to a patient participation (PP) and teaching programme. Follow-up continued by primary care physicians. RESULTS: The mean follow-up was 7.7 years. SC group patients each attended eight annual consultations. The PP patients initiated on average 1.2 +/- 0.8 additional consultations per annum. The relative risk (RR) over 8 years, for the combined cardiovascular event index in the intervention (PP) vs. the control (SC) group was 0.65 (95% CI 0.41-0.89, P = 0.001). Nephropathy developed in 14 vs. 7 patients in the SC and PP groups, respectively, RR 0.50 (95% CI 0.28-0.85, P = 0.02), retinopathy developed in 35 vs. 21 patients, RR 0.60 (95% CI 0.21-0.82, P = 0.03). Throughout the study, period blood pressure, LDL-C and HbA1c were significantly lower in the PP than in the SC patients. CONCLUSION: Well-informed and motivated patients, were more successful in maintaining good control of their risk factors, resulting in reduced cardiovascular risk and slower progression of microvascular disease.

Diabet Med. 2005 Apr;22(4):410-4.

Regular ultrasonographic screening significantly prolongs patency of PTFE grafts.

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BACKGROUND: Polytetrafluoroethylene (PTFE) dialysis grafts have considerably shorter patency than native arteriovenous fistulas, despite the use of a complex of screening monitoring methods (venous pressure, access flow). PTFE grafts are used often in subjects with depleted subcutaneous veins after previous abandoned accesses, so keeping the access patent is crucial. We hypothesized that regular duplex Doppler ultrasound screening for access stenoses, together with their sooner treatment, would prolong PTFE graft patency. METHODS: We performed a randomized, prospective study of PTFE grafts' cumulative patency in 192 subjects. In group 1, regular

ultrasound examinations performed every 3 months was added to traditional screening (i.e., regular access examination at hemodialysis unit, monitoring of venous pressure and access flow). Group 2 was screened only traditionally (without ultrasound). Interventions of suspected stenoses were indicated by nephrologists, vascular surgeon, and, in group 1, also by ultrasonography. Classic ultrasound criteria for significant stenosis were used, even if the access flow had not been decreased. The mean follow-up lasted 392 +/- 430 days. RESULTS: Groups were similar with respect to age, gender, diabetes status, and number of previous abandoned accesses. Group 1 had significantly longer access patency (P < 0.001). Number of interventions per graft was 2.1 +/- 1.8 and 1.3 +/- 1.0 in group 1 and group 2. CONCLUSIONS: Regular screening duplex Doppler ultrasonography results in significantly longer PTFE graft patency due to early detection of access stenosis and, thus, more frequent elective interventions of access stenoses

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Renoprotective action of fenoldopam in high-risk patients undergoing cardiac surgery: a prospective, double-blind, randomized clinical trial.

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BACKGROUND: Acute renal failure is a serious complication of cardiac surgery causing high morbidity and mortality. The aim of this study was to evaluate the usefulness of fenoldopam, a specific agonist of the dopamine-1 receptor, in patients at high risk of perioperative renal dysfunction. METHODS AND RESULTS: A prospective single-center, randomized, double-blind trial was performed after local ethical committee approval and after written consent was obtained from 80 patients undergoing cardiac surgery. Patients received either fenoldopam at 0.05 microg/kg per minute or dopamine at 2.5 microg/kg per minute after the induction of anesthesia for a 24-hour period. All these patients were at high risk of perioperative renal dysfunction as indicated by Continuous Improvement in Cardiac Surgery Program score >10. Primary end point was defined as 25% creatinine increase from baseline levels after cardiac surgery. The 2 groups (fenoldopam versus dopamine) were homogeneous cohorts, and no difference in outcome was observed. Acute renal failure was similar: 17 of 40 (42.5%) in the fenoldopam group and 16 of 40 (40%) in the dopamine group (P=0.9). Peak postoperative serum creatinine level, intensive care unit and hospital stay, and mortality were also similar in the 2 groups. CONCLUSIONS: Despite an increasing number of reports of renal protective properties from fenoldopam, we observed no difference in the clinical outcome compared with dopamine in a high-risk population undergoing cardiac surgery.

Circulation. 2005 Jun 21;111(24):3230-5.

A cognitive behavioral group approach to enhance adherence to hemodialysis fluid restrictions: a randomized controlled trial.

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BACKGROUND: Adhering to fluid restrictions represents one of the most difficult aspects of the hemodialysis treatment regimen. This report describes a randomized controlled trial of a group-based cognitive behavioral intervention aimed at improving fluid-restriction adherence in patients receiving hemodialysis. It was hypothesized that the intervention would improve adherence, measured by means of interdialytic weight gain (IWG), without impacting negatively on psychosocial functioning. METHODS: Fifty-six participants receiving hemodialysis from 4 renal outpatient settings were randomly assigned to an immediate-treatment group (ITG; n = 29) or deferred-treatment group (DTG; n = 27). Participants were assessed at baseline, posttreatment, and follow-up stages. Treatment consisted of a 4-week intervention using educational, cognitive, and behavioral strategies to enhance effective self-management of fluid consumption. RESULTS: No significant difference in mean IWGs was found between the ITG and DTG during the acute-phase analysis ($F(1,54) = 0.03$; $P > 0.05$). However, in longitudinal

analysis, there was a significant main effect for mean IWG ($F(1.76,96.80) = 9.10$; $P < 0.001$) and a significant difference between baseline and follow-up IWG values ($t55 = 3.85$; $P < 0.001$), reflecting improved adherence over time. No adverse effects of treatment were indicated through measures of psychosocial functioning. Some significant changes were evidenced in cognitions thought to be important in mediating behavioral change. CONCLUSION: The current study provides evidence for the feasibility and effectiveness of applying group-based cognitive behavior therapy to enhance adherence to hemodialysis fluid restrictions. Results are discussed in the context of the study's methodological limitations.

Am J Kidney Dis. 2005 Jun;45(6):1046-57.

Comparison of continuous and intermittent renal replacement therapy for acute renal failure.

UEHLINGER DE, JAKOB SM, FERRARI P, EICHELBERGER M, HUYNH-DO U, MARTI HP, MOHAUPT MG, VOGT B, ROTHEN HU, REGLI B, TAKALA J, FREY FJ.

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BACKGROUND: Mortality rates of critically ill patients with acute renal failure (ARF) requiring renal replacement therapy (RRT) are high. Intermittent and continuous RRT are available for these patients on the intensive care units (ICUs). It is unknown which technique is superior with respect to patient outcome. METHODS: We randomized 125 patients to treatment with either continuous venovenous haemodiafiltration (CVVHDF) or intermittent haemodialysis (IHD) from a total of 191 patients with ARF in a tertiary-care university hospital ICU. The primary end-point was ICU and in-hospital mortality, while recovery of renal function and hospital length of stay were secondary end-points. RESULTS: During 30 months, no patient escaped randomization for medical reasons. Sixty-six patients were not randomized for non-medical reasons. Of the 125 randomized patients, 70 were treated with CVVHDF and 55 with IHD. The two groups were comparable at the start of RRT with respect to age (62+/-15 vs 62+/-15 years, CVVHDF vs IHD), gender (66 vs 73% male sex), number of failed organ systems (2.4+/-1.5 vs 2.5+/-1.6), Simplified Acute Physiology Scores (57+/-17 vs 58+/-23), septicaemia (43 vs 51%), shock (59 vs 58%) or previous surgery (53 vs 45%). Mortality rates in the hospital (47 vs 51%, CVVHDF vs IHD, $P = 0.72$) or in the ICU (34 vs 38%, $P = 0.71$) were independent of the technique of RRT applied. Hospital length of stay in the survivors was comparable in patients on CVVHDF [median (range) 20 (6-71) days, $n = 36$] and in those on IHD [30 (2-89) days, $n = 27$, $P = 0.25$]. The duration of RRT required was the same in both groups. CONCLUSION: The present investigation provides no evidence for a survival benefit of continuous vs intermittent RRT in ICU patients with ARF.

Nephrol Dial Transplant. 2005 Aug;20(8):1630-7.

Comparison of continuous and intermittent renal replacement therapy for acute renal failure.

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